

## Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTANXR1625

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* \* \* \* \* \* \* \* \* Welcome to STN International \* \* \* \* \* \* \* \* \* \* \* \*

NEWS 1 Web Page for STN Seminar Schedule - N. America  
NEWS 2 JAN 08 CHEMLIST enhanced with New Zealand Inventory of Chemicals  
NEWS 3 JAN 16 CA/CAplus Company Name Thesaurus enhanced and reloaded  
NEWS 4 JAN 16 IPC version 2007.01 thesaurus available on STN  
NEWS 5 JAN 16 WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data  
NEWS 6 JAN 22 CA/CAplus updated with revised CAS roles  
NEWS 7 JAN 22 CA/CAplus enhanced with patent applications from India  
NEWS 8 JAN 29 PHAR reloaded with new search and display fields  
NEWS 9 JAN 29 CAS Registry Number crossover limit increased to 300,000 in multiple databases  
NEWS 10 FEB 15 PATDPASPC enhanced with Drug Approval numbers  
NEWS 11 FEB 15 RUSSIAPAT enhanced with pre-1994 records  
NEWS 12 FEB 23 KOREAPAT enhanced with IPC 8 features and functionality  
NEWS 13 FEB 26 MEDLINE reloaded with enhancements  
NEWS 14 FEB 26 EMBASE enhanced with Clinical Trial Number field  
NEWS 15 FEB 26 TOXCENTER enhanced with reloaded MEDLINE  
NEWS 16 FEB 26 IFICDB/IFIPAT/IFIUDB reloaded with enhancements  
NEWS 17 FEB 26 CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases  
NEWS 18 MAR 15 WPIDS/WPIX enhanced with new FRAGHITSTR display format  
NEWS 19 MAR 16 CASREACT coverage extended  
NEWS 20 MAR 20 MARPAT now updated daily  
NEWS 21 MAR 22 LWPI reloaded  
NEWS 22 MAR 30 RDISCLOSURE reloaded with enhancements  
NEWS 23 APR 02 JICST-EPLUS removed from database clusters and STN  
NEWS 24 APR 30 GENBANK reloaded and enhanced with Genome Project ID field  
NEWS 25 APR 30 CHEMCATS enhanced with 1.2 million new records  
NEWS 26 APR 30 CA/CAplus enhanced with 1870-1889 U.S. patent records  
NEWS 27 APR 30 INPADOC replaced by INPADOCDB on STN  
NEWS 28 MAY 01 New CAS web site launched  
NEWS 29 MAY 08 CA/CAplus Indian patent publication number format defined  
NEWS 30 MAY 11 RDISCLOSURE on STN Easy enhanced with new search and display fields  
NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

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Enter NEWS followed by the item number or name to see news on that specific topic.

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FILE 'HOME' ENTERED AT 09:50:30 ON 14 MAY 2007

FILE 'REGISTRY' ENTERED AT 09:50:50 ON 14 MAY 2007  
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STRUCTURE FILE UPDATES: 13 MAY 2007 HIGHEST RN 934672-05-6  
DICTIONARY FILE UPDATES: 13 MAY 2007 HIGHEST RN 934672-05-6

New CAS Information Use Policies. enter HELP USAGETERMS for details.

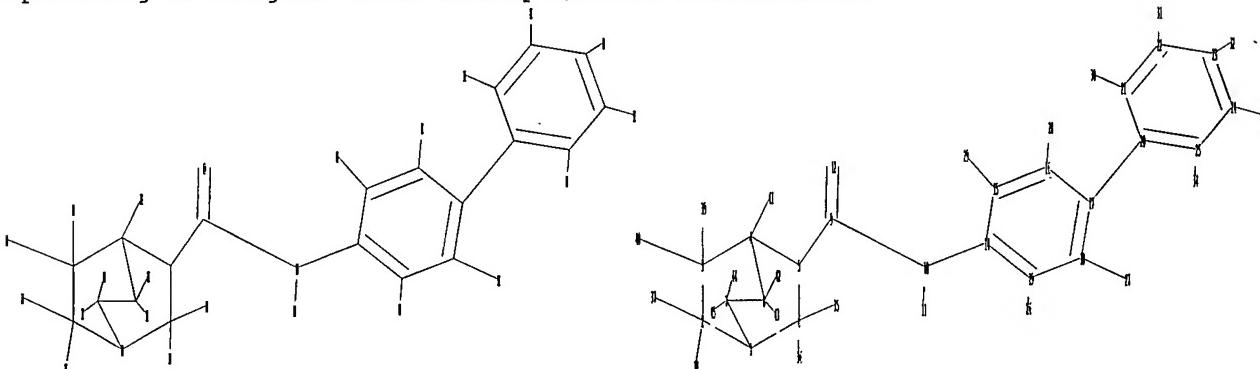
TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=>  
Uploading C:\Program Files\Stnexp\Queries\10565181.str



chain nodes :

Chain Nodes : 9 10 11 12 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42

5 10 11

43 44 45  
ring nodes :

Ping nodes :

1 2 3 4 5  
absent band

chain bonds :  
 2-37 2-38 3-39 3-40 4-41 5-9 6-35 6-36 7-44 7-45 8-42 8-43 9-10 9-12  
 10-11 10-14 15-29 16-28 17-20 18-27 19-26 21-30 22-31 23-32 24-33 25-34

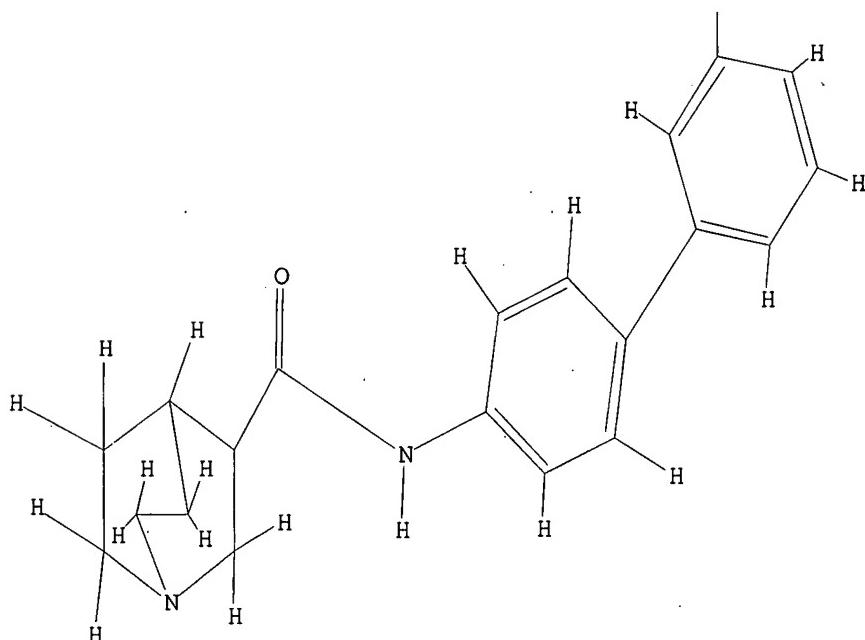
ring bonds :  
 1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6 7-8 14-15 14-19 15-16 16-17 17-18  
 18-19 20-21 20-25 21-22 22-23 23-24 24-25  
 exact/norm bonds :  
 1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6 7-8 9-10 9-12 10-14  
 exact bonds :  
 2-37 2-38 3-39 3-40 4-41 5-9 6-35 6-36 7-44 7-45 8-42 8-43 10-11 15-29  
 16-28 17-20 18-27 19-26 21-30 22-31 23-32 24-33 25-34  
 normalized bonds :  
 14-15 14-19 15-16 16-17 17-18 18-19 20-21 20-25 21-22 22-23 23-24 24-25  
 isolated ring systems :  
 containing 1 : 14 : 20 :

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:CLASS 10:CLASS  
 11:CLASS 12:CLASS 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom  
 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:CLASS 27:CLASS 28:CLASS 29:CLASS  
 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS  
 38:CLASS 39:CLASS 40:CLASS 41:CLASS 42:CLASS 43:CLASS 44:CLASS 45:CLASS

L1 STRUCTURE UPLOADED

=> d 11  
 L1 HAS NO ANSWERS  
 L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 11  
 SAMPLE SEARCH INITIATED 09:51:54 FILE 'REGISTRY'  
 SAMPLE SCREEN SEARCH COMPLETED - 7 TO ITERATE

100.0% PROCESSED 7 ITERATIONS 0 ANSWERS  
 SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 7 TO 298  
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s 11 full  
FULL SEARCH INITIATED 09:51:58 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 165 TO ITERATE

100.0% PROCESSED 165 ITERATIONS 0 ANSWERS  
SEARCH TIME: 00.00.01

L3 0 SEA SSS FUL L1

=> log y  
COST IN U.S. DOLLARS SINCE FILE TOTAL  
FULL ESTIMATED COST ENTRY SESSION  
172.55 172.76

STN INTERNATIONAL LOGOFF AT 09:52:03 ON 14 MAY 2007

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTANXR1625

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* \* \* \* \* \* Welcome to STN International \* \* \* \* \* \* \* \* \*

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NEWS 24 APR 30 GENBANK reloaded and enhanced with Genome Project ID field  
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NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.  
  
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NEWS LOGIN Welcome Banner and News Items  
NEWS IPC8 For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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FILE 'HOME' ENTERED AT 09:55:56 ON 14 MAY 2007

FILE 'REGISTRY' ENTERED AT 09:56:11 ON 14 MAY 2007  
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STRUCTURE FILE UPDATES: 13 MAY 2007 HIGHEST RN 934672-05-6  
DICTIONARY FILE UPDATES: 13 MAY 2007 HIGHEST RN 934672-05-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

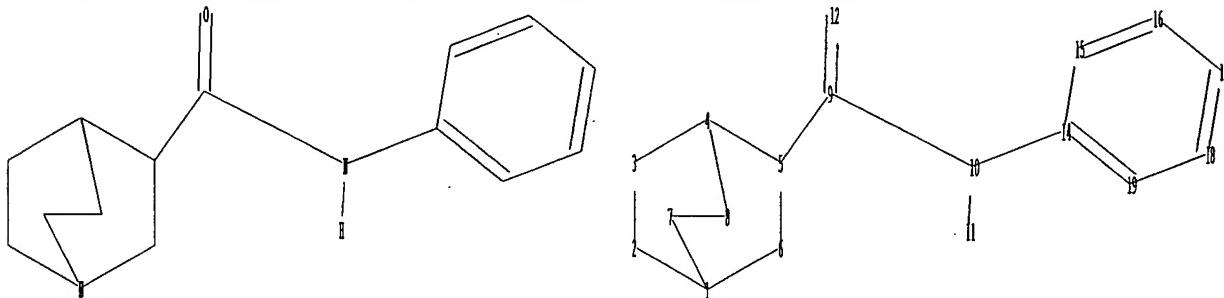
Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/support/stngen/stndoc/properties.html>

=>

Uploading C:\Program Files\Stnexp\Queries\10565181a.str



```

chain nodes :
9 10 11 12
ring nodes :
1 2 3 4 5 6 7 8 14 15 16 17 18 19
chain bonds :
5-9 9-10 9-12 10-11 10-14
ring bonds :
1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6 7-8 14-15 14-19 15-16 16-17 17-18
18 19
exact/norm bonds :
1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6 7-8 9-10 9-12 10-14
exact bonds :

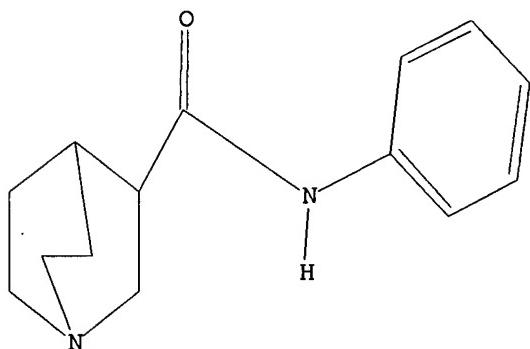
```

5-9 10-11  
normalized bonds :  
14-15 14-19 15-16 16-17 17-18 18-19  
isolated ring systems :  
containing 1 : 14 :

Match level :  
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:CLASS 10:CLASS  
11:CLASS 12:CLASS 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom

L1 STRUCTURE UPLOADED

=> d 11  
L1 HAS NO ANSWERS  
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 11  
SAMPLE SEARCH INITIATED 09:56:38 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 366 TO ITERATE  
  
100.0% PROCESSED 366 ITERATIONS 3 ANSWERS  
SEARCH TIME: 00.00.01  
  
FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 6173 TO 8467  
PROJECTED ANSWERS: 3 TO 162

L2 3 SEA SSS SAM L1

=> s11 full  
SL1 IS NOT A RECOGNIZED COMMAND  
The previous command name entered was not recognized by the system.  
For a list of commands available to you in the current file, enter  
"HELP COMMANDS" at an arrow prompt (>).

=> s 11 full  
FULL SEARCH INITIATED 09:56:48 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED 7468 TO ITERATE

100.0% PROCESSED 7468 ITERATIONS 79 ANSWERS  
SEARCH TIME: 00.00.01

L3

79 SEA SSS FUL L1

=> file caplus  
COST IN U.S. DOLLARS  
SINCE FILE  
ENTRY  
TOTAL  
SESSION  
FULL ESTIMATED COST  
172.10  
172.31

FILE 'CAPLUS' ENTERED AT 09:56:54 ON 14 MAY 2007  
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FILE COVERS 1907 - 14 May 2007 VOL 146 ISS 21  
FILE LAST UPDATED: 13 May 2007 (20070513/ED)

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<http://www.cas.org/infopolicy.html>

=> s 13 full  
L4 13 L3

=> d ibib abs hitstr tot

L4 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2005:120928 CAPLUS  
DOCUMENT NUMBER: 142:198251  
TITLE: Preparation of quinuclidine N-biaryl amides for use in treatment and/or prophylaxis of diseases  
INVENTOR(S): Flessner, Timo; Boess, Frank-Gerhard; Hafner, Frank-Thorsten; Luithle, Joachim; Methfessel, Christoph; Telan, Leila  
PATENT ASSIGNEE(S): Bayer Healthcare AG, Germany  
SOURCE: PCT Int. Appl., 51 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005012299	A1	20050210	WO 2004-EP8037	20040719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LU, NZ, OM, PG, PL, PT, RU, SC, SD, SE, SG, SN, SL, SI, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,				

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10334724 .	A1	20050224	DE 2003-10334724	20030730
CA 2534003	A1	20050210	CA 2004-2534003	20040719
EP 1651645	A1	20060503	EP 2004-741132	20040719
EP 1651645	B1	20070221		
R: DE, ES, FR, GB, IT				
JP 2007500152	T	20070111	JP 2006-521462	20040719
PRIORITY APPLN. INFO.:			DE 2003-10334724	A 20030730
			WO 2004-EP8037	W 20040719
OTHER SOURCE(S):	CASREACT	142:198251;	MARPAT	142:198251
GI				

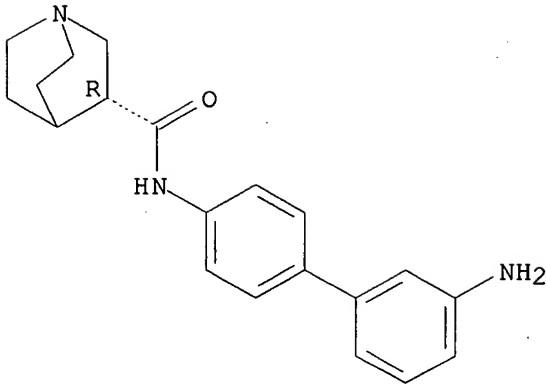
\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The invention relates to N-biaryl amides I [R1 = NR2CONR3R4, NR2COCO2R5, NHSO2R6, SO2NHR7, NHCOR8; R2 = H, C1-6-alkyl; R3, R4 = H, C1-6-alkyl, C3-8-cycloalkyl, Ph (optionally substituted with up to three residues from the group halogen, CN, C1-6-alkyl, C1-6-alkoxy, CF3, OCF3); NR3R4 = 5- or 6-membered ring; R5 = H, C1-6-alkyl, C3-8-cycloalkyl, aryl, aryl-(C1-6-alkyl), R6 = C1-6-alkyl, C3-8-cycloalkyl, 5- or 6-membered heterocycle or heteroaryl, aryl-(C1-6-alkyl); R7 = C1-6-alkyl, C3-8-cycloalkyl, aryl, 5- or 6-membered heterocycle or heteroaryl, aryl-(C1-6-alkyl); R8 = C1-6-alkyl, C3-8-cycloalkyl, Ph, Ph-(C1-6-alkyl), (C1-6-alkoxy)-(C1-6-alkyl), (optionally substituted with up to three residues from the group halogen, CN, C1-6-alkyl, C1-6-alkoxy, CF3, OCF3)], their salts, solvates and salt solvates, methods for their production and use thereof for the production of medicaments for the treatment and/or prophylaxis of diseases and for improvement in cognition, concentration power, learning power and/or memory. Procedure for the preparation of I comprises: amidation of quinuclidine II [X = OH, Cl, OC6F5] with amines III or IV [Y = triflate, halogen (especially Br or I)]; with the latter, intermediate V is formed and is coupled with boronic acid VI [R9 = H, Me; (R9)2 = CH2CH2, CMe2CMe2] in an inert solvent containing a catalyst and a base. Thus, I·HCl [R1 = NHSO2Me-4] was prepared from quinuclidin-3-one via deoxidative cyanation, chromatog. resolution, hydrolysis, carbonyl chlorination and amidation with 4-(4-H2NC6H4)C6H4NHSO2Me. The binding ability of I·HCl [R1 = NHSO2Me-4] towards 7 $\alpha$ -n acetylcholine receptor was determined [Ki = 2 nM].

IT 838852-86-1P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation and acylation, sulfonation or carbamylation of; preparation of quinuclidine N-biaryl amides for use in treatment and/or prophylaxis of diseases)

RN 838852-86-1 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(3'-amino[1,1'-biphenyl]-4-yl)-, dihydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

IT 838852-85-0P

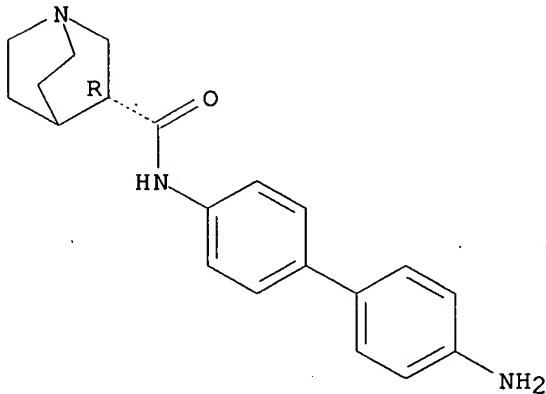
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and acylation, sulfonylation or carbamylation of; preparation of

quinuclidine N-biaryl amides for use in treatment and/or prophylaxis of diseases)

RN 838852-85-0 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4'-amino[1,1'-biphenyl]-4-yl)-, dihydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 HCl

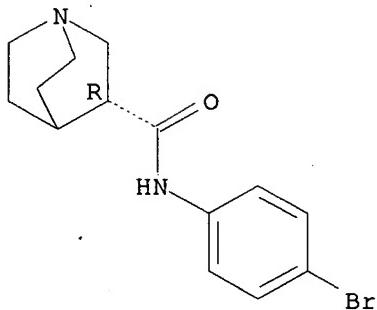
IT 604803-85-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and coupling reactions of, with boronates; preparation of quinuclidine N-biaryl amides for use in treatment and/or prophylaxis of

RN 604803-85-2 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4-bromophenyl)-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



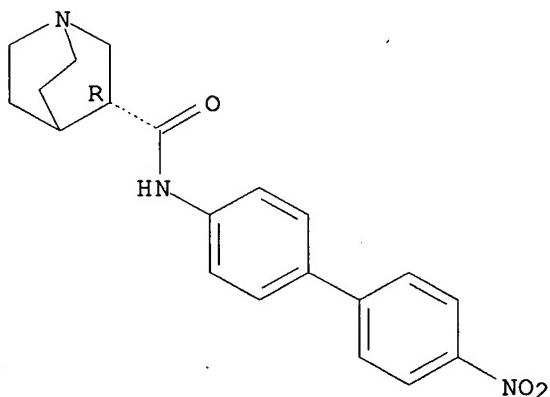
IT 838852-84-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(preparation and hydrogenolysis of; preparation of quinuclidine N-biaryl amides  
for use in treatment and/or prophylaxis of diseases)

RN 838852-84-9 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4'-nitro[1,1'-biphenyl]-4-yl)-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

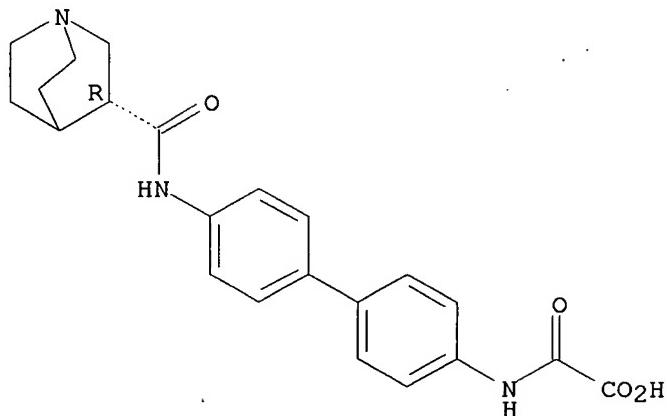
IT 838852-67-8P 838852-68-9P 838852-69-0P  
838852-70-3P 838852-71-4P 838852-72-5P  
838852-73-6P 838852-74-7P 838852-75-8P  
838852-76-9P 838852-77-0P 838852-78-1P  
838852-79-2P 838852-80-5P 838852-81-6P  
838852-82-7P 838852-83-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of quinuclidine N-biaryl amides for use in treatment and/or prophylaxis of diseases)

DN 838852-67-8 CAPLUS

CN Acetic acid, [(4'-(3R)-1-azabicyclo[2.2.2]octane-3-yloxy)amino]biphenyl-4-yl]amino]oxo-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

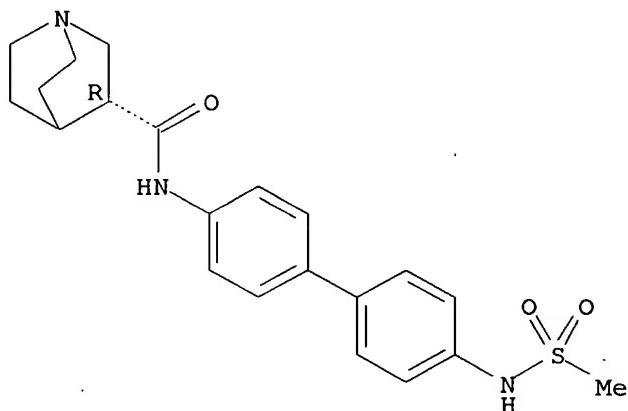


● HCl

RN 838852-68-9 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(methylsulfonyl)amino][1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

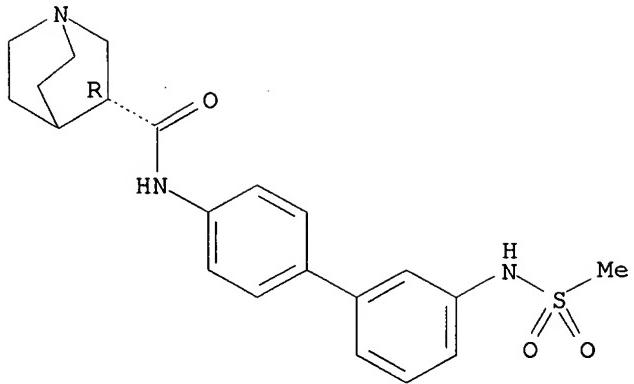


● HCl

RN 838852-69-0 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[3'-(methylsulfonyl)amino][1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

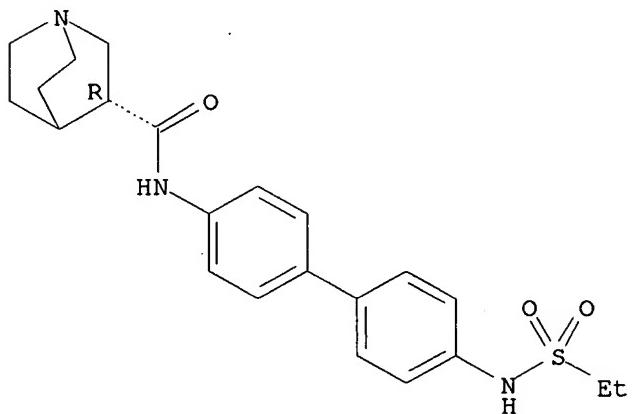


● HCl

RN 838852-70-3 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(ethylsulfonyl)amino][1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

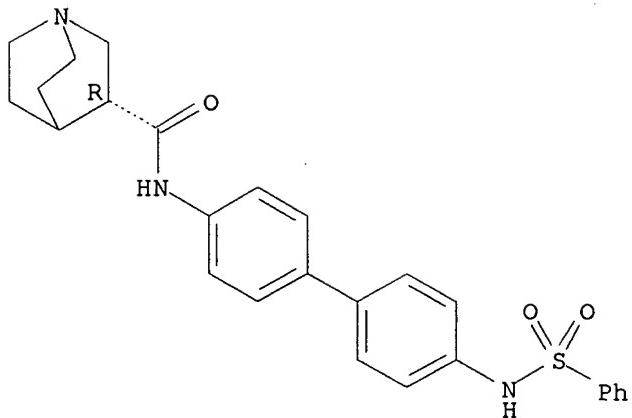


● HCl

RN 838852-71-4 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(phenylsulfonyl)amino][1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

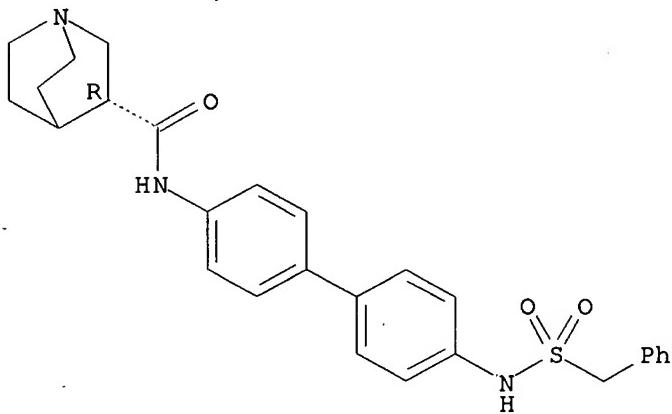


● HCl

RN 838852-72-5 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-([(phenylmethyl)sulfonyl]amino)[1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

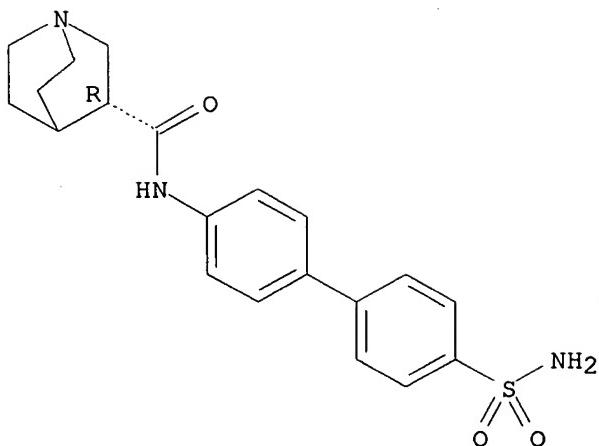


● HCl

RN 838852-73-6 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(aminosulfonyl)[1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

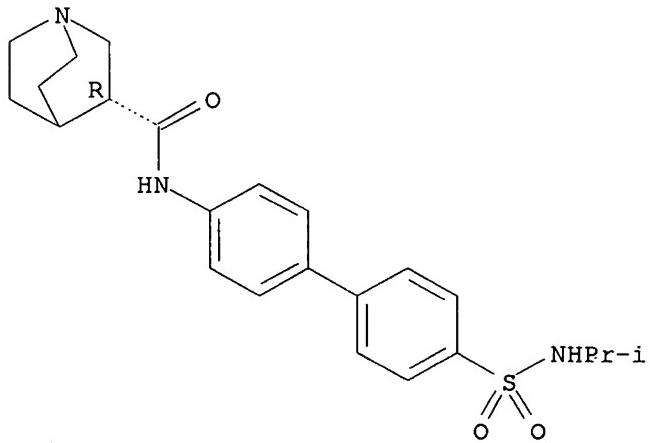


● HCl

RN 838852-74-7 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-([(1-methylethyl)amino]sulfonyl)[1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

## Absolute stereochemistry.

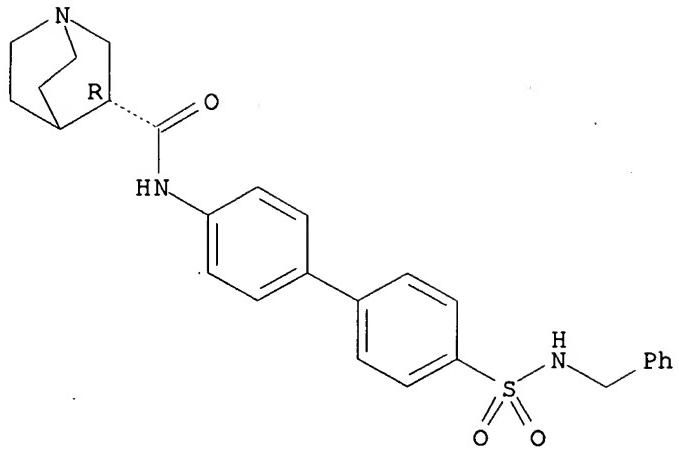


● HCl

RN 838852-75-8 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-([(phenylmethyl)amino]sulfonyl)[1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

## Absolute stereochemistry.

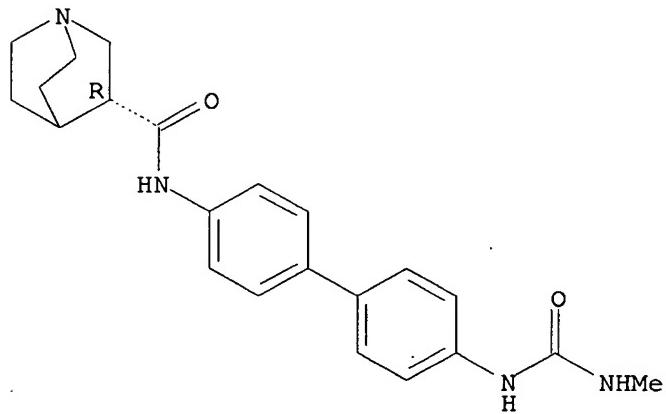


● HCl

RN 838852-76-9 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-
 [[(methylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

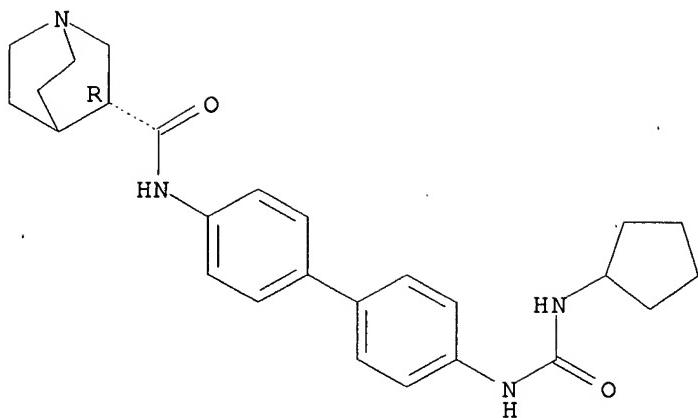
Absolute stereochemistry.



RN 838852-77-0 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-
 [[(cyclopentylamino)carbonyl]amino][1,1'-biphenyl]-4-yl]-,
 monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

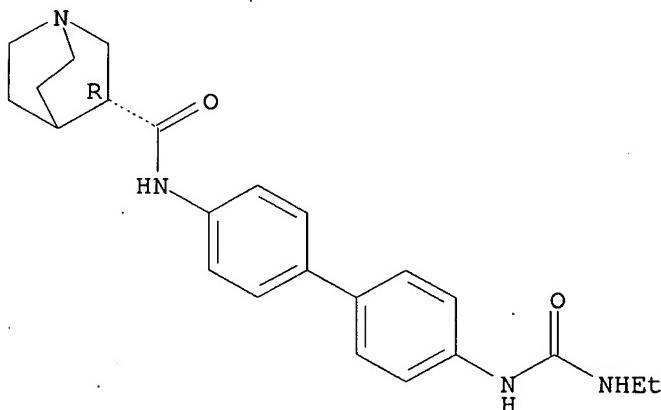


● HCl

RN 838852-78-1 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-([(ethylamino)carbonyl]amino)[1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

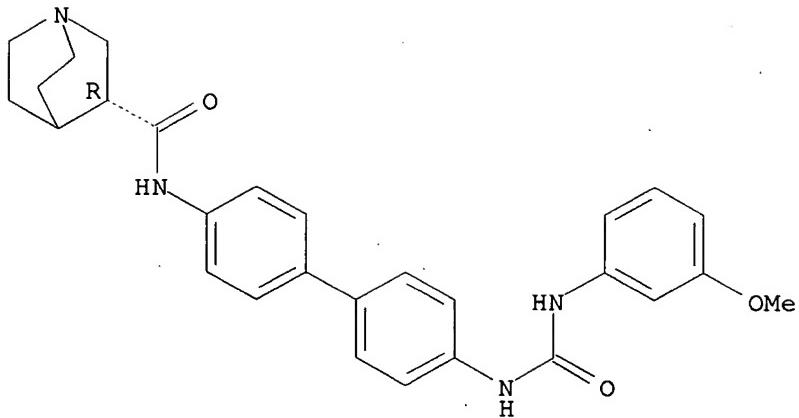
Absolute stereochemistry.



RN 838852-79-2 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-[[[(3-methoxyphenyl)amino]carbonyl]amino][1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

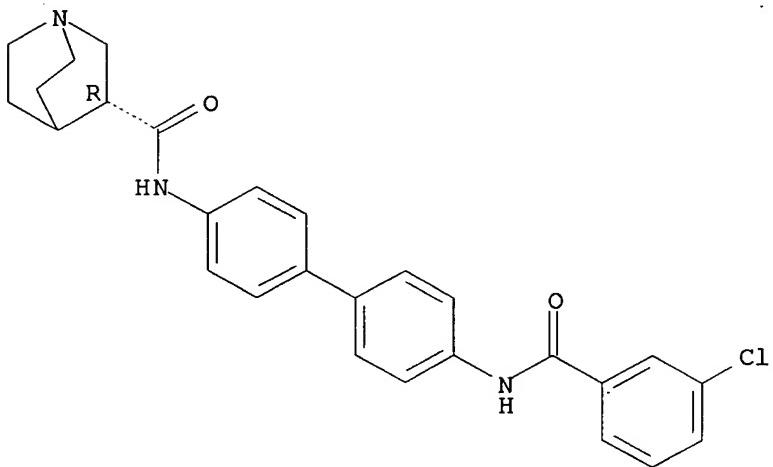


● HCl

RN 838852-80-5 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(3-chlorobenzoyl)amino][1,1'-biphenyl]-4-yl-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

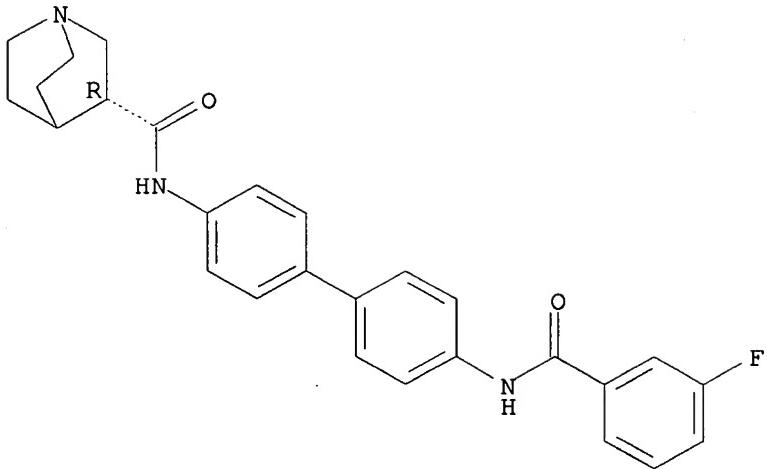


● HCl

RN 838852-81-6 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(3-fluorobenzoyl)amino][1,1'-biphenyl]-4-yl-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

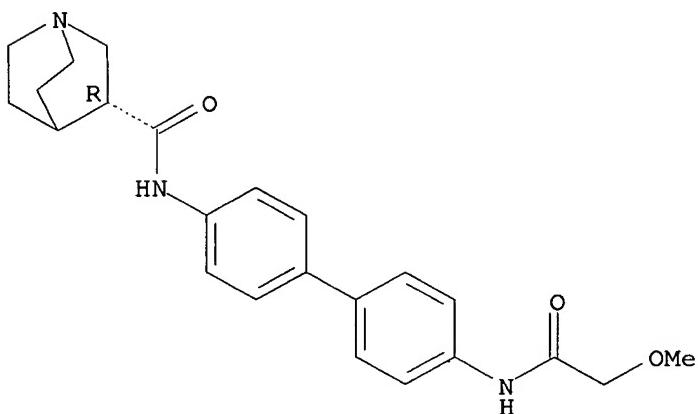


● HCl

RN 838852-82-7 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(methoxyacetyl)amino][1,1'-biphenyl]-4-yl-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

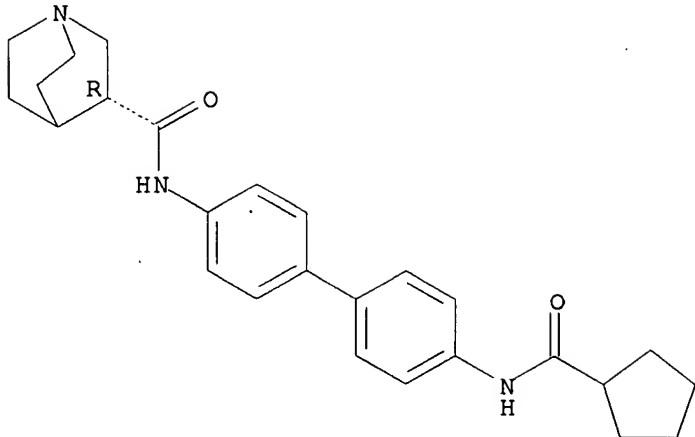


● HCl

RN 838852-83-8 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(cyclopentylcarbonyl)amino][1,1'-biphenyl]-4-yl-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

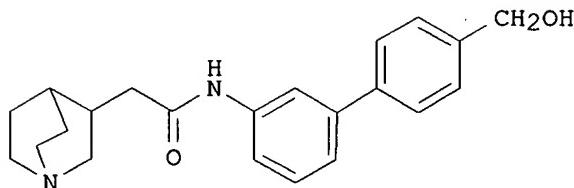
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2003:757707 CAPLUS  
 DOCUMENT NUMBER: 139:277050  
 TITLE: Preparation of aza-bicyclic N-biaryl amides with affinity for the  $\alpha_7$ -nicotinic acetylcholine receptor  
 INVENTOR(S): Luithle, Joachim; Boess, Frank-Gerhard; Erb, Christina; Schnizler, Katrin; Flessner, Timo; Van Kampen, Marja; Methfessel, Christoph; Hafner, Frank-Thorsten  
 PATENT ASSIGNEE(S): Bayer Aktiengesellschaft, Germany  
 SOURCE: PCT Int. Appl., 75 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003078431	A1	20030925	WO 2003-EP2153	20030303
WO 2003078431	A8	20041104		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10211415	A1	20030925	DE 2002-10211415	20020315
EP 1487834	A1	20041222	EP 2003-708168	20030303
EP 1487834	B1	20070425		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK  
 US 2005154045 A1 20050714 US 2003-508108 20030303  
 US 7138410 B2 20061121  
 JP 2005524675 T 20050818 JP 2003-576436 20030303  
 PRIORITY APPLN. INFO.: DE 2002-10211415 A 20020315  
 WO 2003-EP2153 W 20030303

OTHER SOURCE(S): MARPAT 139:277050  
GI



**AB** The azabicyclic N-arylamides, R<sub>1</sub>AC(:O)NR<sub>3</sub>ER<sub>3</sub> [R<sub>1</sub> = 1-azabicyclo[m.n.p]alkyl (7 - 11 ring atoms, optionally substituted with C1-6-alkyl); m, n = 2, 3; p = 1, 2, 3; A = CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, propylene; E = 5-6 membered heteroaryl of benzenediyl optionally substituted with halo, cyano, F<sub>3</sub>C, F<sub>3</sub>CO, C1-6-alkyl; R<sub>2</sub> = 5-6 membered heteroaryl, Ph, optionally substituted with halo, heterocyclyl, carbamoyl, carboxylate, amino, acyl, CN, CF<sub>3</sub>, CF<sub>3</sub>O, NO<sub>2</sub>, C1-6-alkyl, C1-6-alkoxy, C1-6-alkylthio, etc.; R<sub>3</sub> = H, C1-6-alkyl] and their salts, solvates and salt solvates were prepared and used for producing pharmaceuticals for the treatment and/or prophylaxis of diseases and for improving perception, concentration, learning ability and memory. Thus, 2-(1-azabicyclo[2.2.2]octan-3-yl)-N-(3-bromophenyl)acetamide hydrochloride was treated with 4-(hydroxymethyl)phenylboronic acid to give the quinuclidineacetamide derivative I. The affinity of I for  $\alpha$ -nAChR was determined

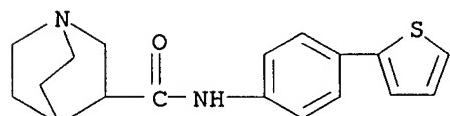
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 604803-25-0P 604803-34-1P 604803-35-2P  
 604803-36-3P 604803-37-4P 604803-38-5P  
 604803-39-6P 604803-40-9P 604803-41-0P  
 604803-42-1P 604803-44-3P 604803-45-4P  
 604803-47-6P 604803-49-8P 604803-97-6P  
 604804-00-4P 604804-02-6P 604804-04-8P

**RL:** PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of aza-bicyclic N-biaryl amides with affinity for  $\alpha$ -7 nicotinic acetylcholine receptor)

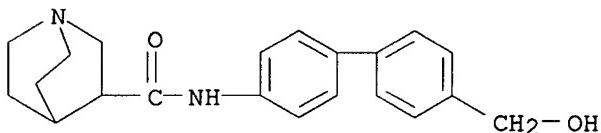
**RN** 604803-22-7 CAPLUS

**CN** 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4-(2-thienyl)phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



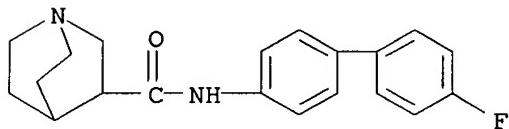
● HCl

RN 604803-23-8 CAPLUS  
CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(hydroxymethyl)[1,1'-biphenyl]-4-yl]-, monohydrochloride (9CI) (CA INDEX NAME)



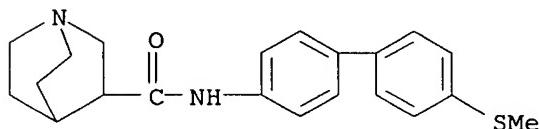
● HCl

RN 604803-24-9 CAPLUS  
CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4'-fluoro[1,1'-biphenyl]-4-yl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

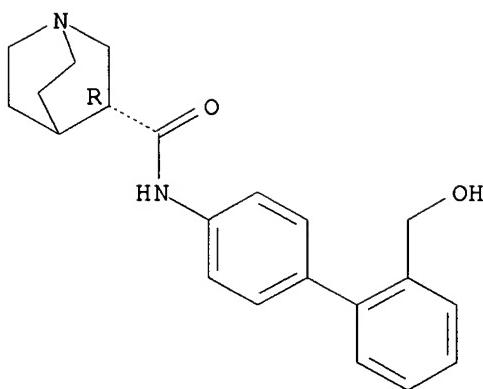
RN 604803-25-0 CAPLUS  
CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(methylthio)[1,1'-biphenyl]-4-yl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RN 604803-34-1 CAPLUS  
CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[2'-(hydroxymethyl)[1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

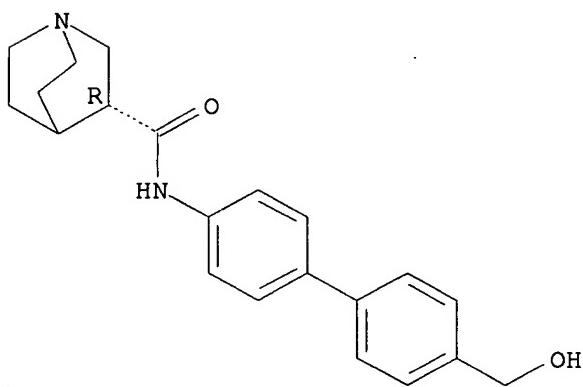
Absolute stereochemistry.



RN 604803-35-2 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(hydroxymethyl)[1,1'-biphenyl]-4-yl]-, monohydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

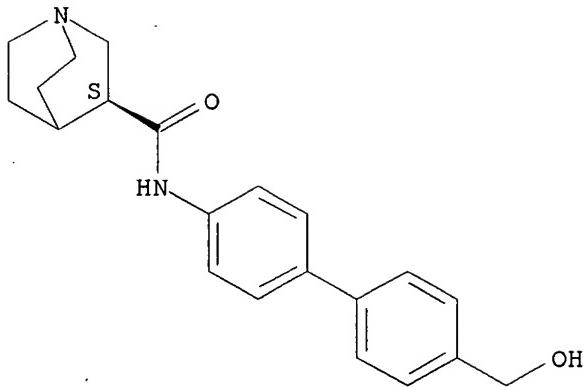


● HCl

RN 604803-36-3 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(hydroxymethyl)[1,1'-biphenyl]-4-yl]-, monohydrochloride, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

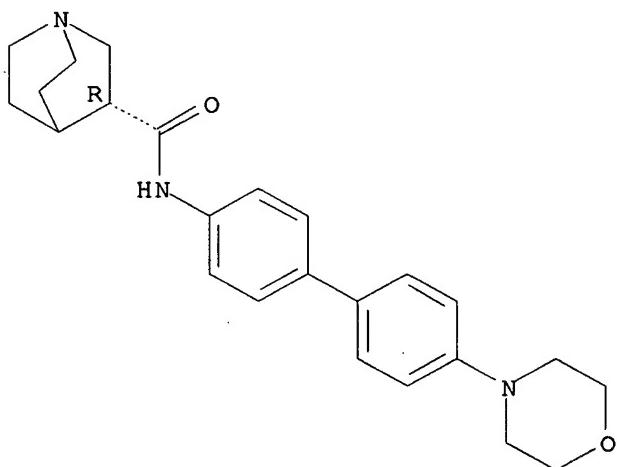


● HCl

RN 604803-37-4 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(4-morpholinyl)[1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

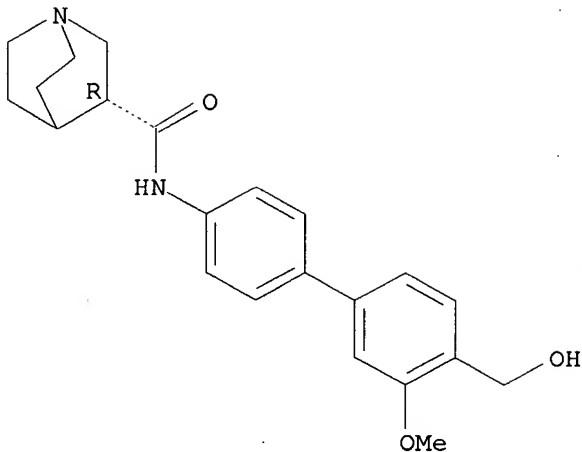
Absolute stereochemistry.



RN 604803-38-5 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(hydroxymethyl)-3'-methoxy[1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

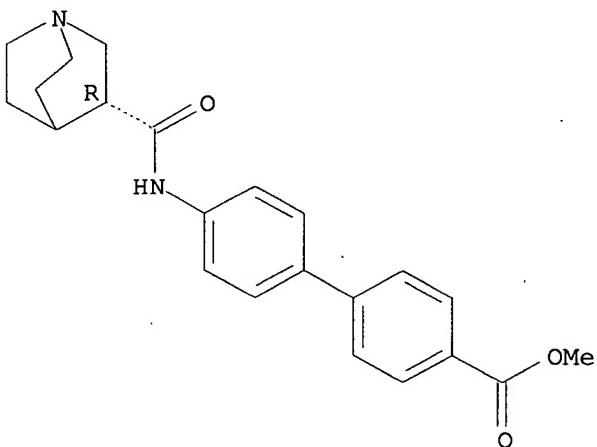
Absolute stereochemistry.



RN 604803-39-6 CAPLUS

CN [1,1'-Biphenyl]-4-carboxylic acid, 4'-[[(3R)-1-azabicyclo[2.2.2]oct-3-ylcarbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)

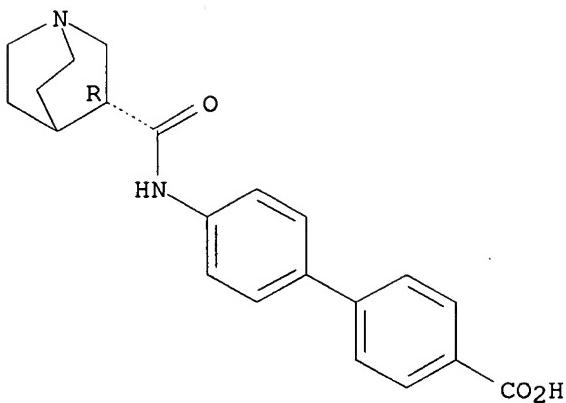
Absolute stereochemistry.



RN 604803-40-9 CAPLUS

CN [1,1'-Biphenyl]-4-carboxylic acid, 4'-[[(3R)-1-azabicyclo[2.2.2]oct-3-ylcarbonyl]amino]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

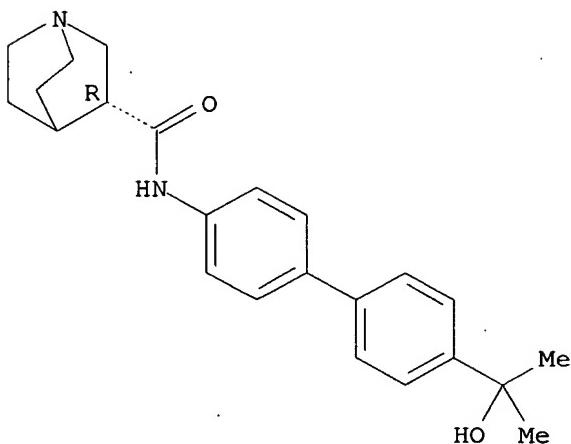


● HCl

RN 604803-41-0 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(1-hydroxy-1-methylethyl)[1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

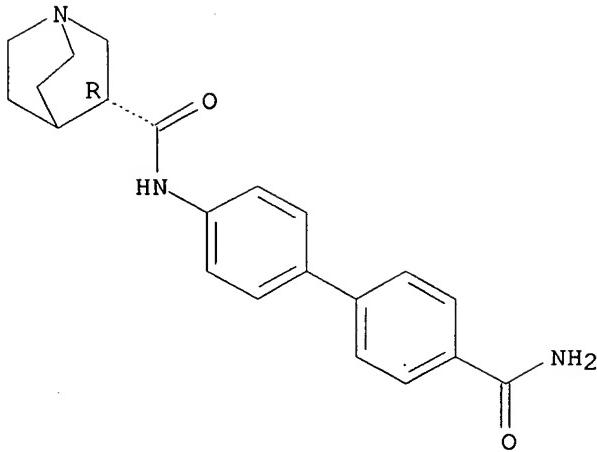
Absolute stereochemistry.



RN 604803-42-1 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(aminocarbonyl)[1,1'-biphenyl]-4-yl]-, hydrochloride, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

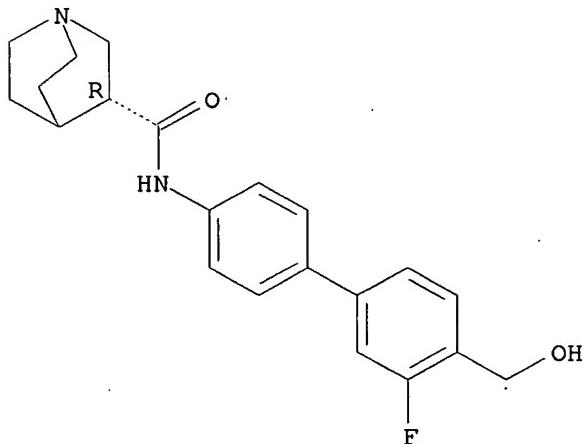


● x HCl

RN 604803-44-3 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[3'-fluoro-4'-(hydroxymethyl)[1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

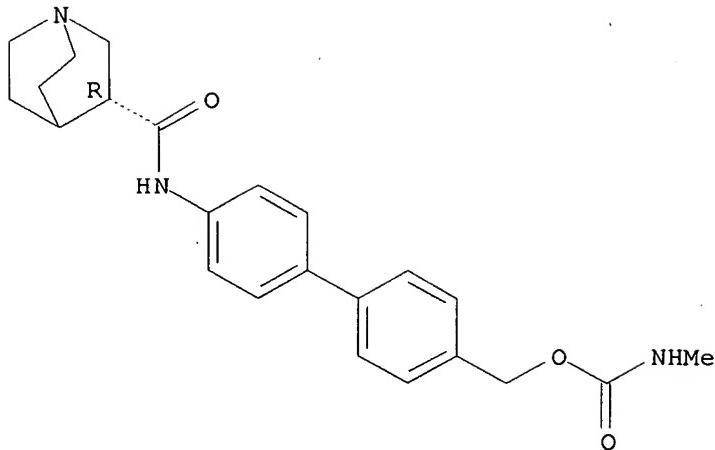
Absolute stereochemistry.



RN 604803-45-4 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-[[[[(methylamino)carbonyl]oxy]methyl][1,1'-biphenyl]-4-yl]-, (3R)- (9CI) (CA INDEX NAME)

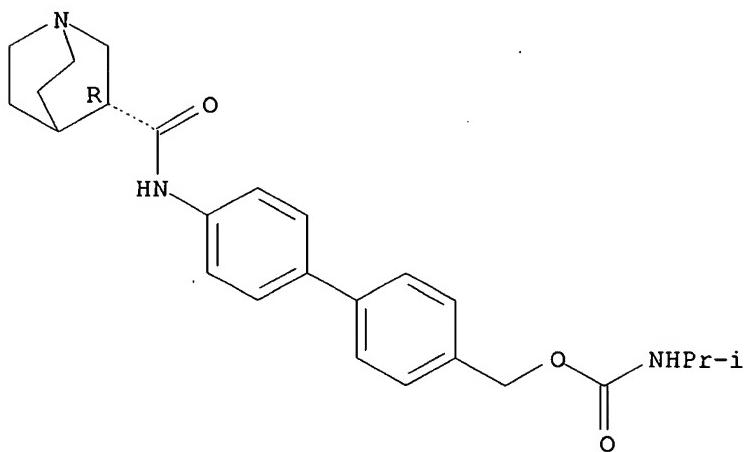
Absolute stereochemistry.



RN 604803-47-6 CAPLUS

CN Carbamic acid, (1-methylethyl)-, [4'--[[(3R)-1-azabicyclo[2.2.2]oct-3-ylcarbonyl]amino][1,1'-biphenyl]-4-yl]methyl ester (9CI) (CA INDEX NAME)

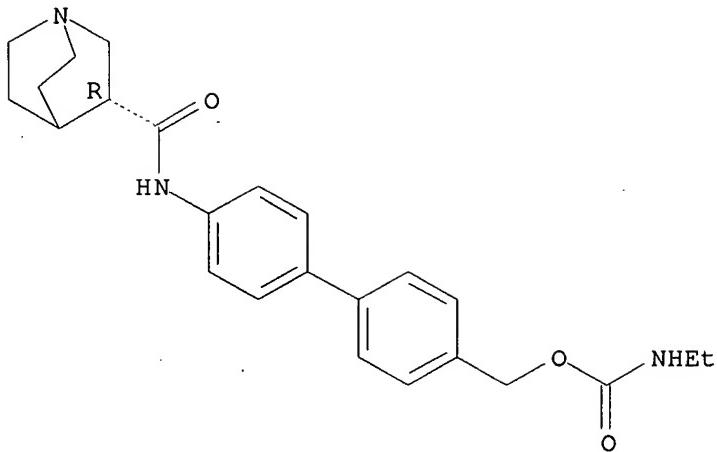
Absolute stereochemistry.



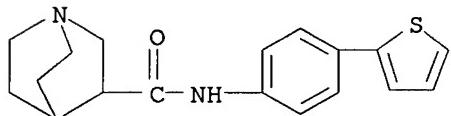
RN 604803-49-8 CAPLUS

CN Carbamic acid, ethyl-, [4'--[[(3R)-1-azabicyclo[2.2.2]oct-3-ylcarbonyl]amino][1,1'-biphenyl]-4-yl]methyl ester (9CI) (CA INDEX NAME)

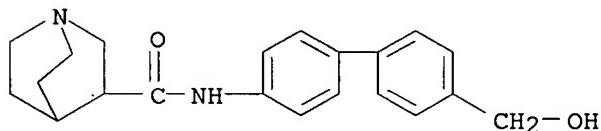
Absolute stereochemistry.



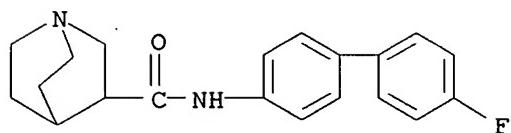
RN 604803-97-6 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4-(2-thienyl)phenyl]- (9CI)  
 (CA INDEX NAME)



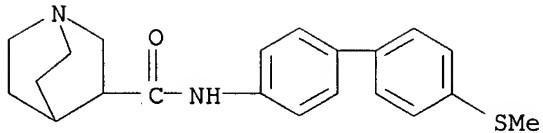
RN 604804-00-4 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(hydroxymethyl)[1,1'-biphenyl]-4-yl]- (9CI) (CA INDEX NAME)



RN 604804-02-6 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4'-fluoro[1,1'-biphenyl]-4-yl)- (9CI) (CA INDEX NAME)

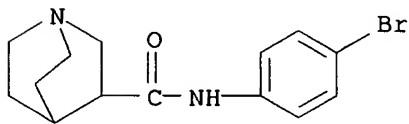


RN 604804-04-8 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4'-(methylthio)[1,1'-biphenyl]-4-yl]- (9CI) (CA INDEX NAME)



IT 604803-72-7P 604803-83-0P 604803-85-2P  
 604804-18-4P  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (preparation of aza-bicyclic N-biaryl amides with affinity for  $\alpha$ -7 nicotinic acetylcholine receptor)

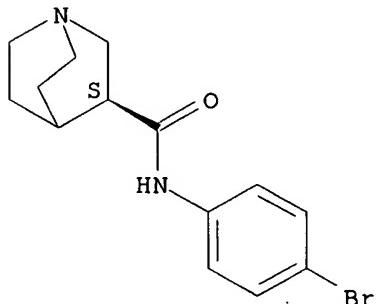
RN 604803-72-7 CAPPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4-bromophenyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

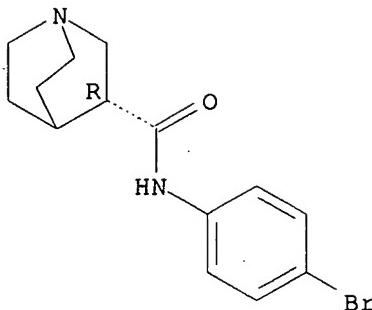
RN 604803-83-0 CAPPLUS  
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Absolute stereochemistry.

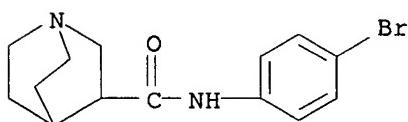


RN 604803-85-2 CAPPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4-bromophenyl)-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



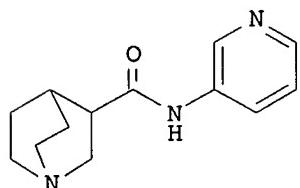
RN 604804-18-4 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(4-bromophenyl)- (9CI) (CA  
 INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2003:506550 CAPLUS  
 DOCUMENT NUMBER: 139:85529  
 TITLE: Preparation of monocyclic N-aryl amides for  
 improvement of the perception and memory enhancement  
 Luithle, Joachim; Boess, Frank-Gerhard; Erb,  
 Christina; Flessner, Timo; Hendrix, Martin; Van  
 Kampen, Marja; Methfessel, Christoph  
 INVENTOR(S):  
 PATENT ASSIGNEE(S): Bayer AG, Germany  
 SOURCE: Ger. Offen., 10 pp.  
 CODEN: GWXXBX  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10162442	A1	20030703	DE 2001-10162442	20011219
PRIORITY APPLN. INFO.:			DE 2001-10162442	20011219
OTHER SOURCE(S):	MARPAT	139:85529		
GI				



AB The invention concerns the use of monocyclic N-aryl amides, R<sub>1</sub>CONR<sub>2</sub>R<sub>3</sub> [R<sub>1</sub> = 1-azabicyclo[m.n.p]alkyl (7 - 11 ring atoms, optionally substituted with C1-6-alkyl); m, n = 2 , 3; p = 1 - 3; R<sub>2</sub> = (un)substituted Ph, 5 to 6-membered heteroaryl (optionally substituted with halogen, CHO, CONH<sub>2</sub>, CN, CF<sub>3</sub>,CF<sub>3</sub>O, NO<sub>2</sub>, C1-6-alkyl, C1-6-alkoxy, C1-6-alkylthio); R<sub>3</sub> = H, C1-6-alkyl] and their salts, solvates and solvate salts, in the production of drugs for the improvement of the perception, concentration achievement, learning

achievement and/or memory achievement as well as to new monocyclic N-aryl amides. Thus, N-(3-pyridinyl)quinuclidine-3-carboxamide dihydrochloride(I·2HCl) was prepared from quinuclidine-3-carboxylic acid chloride hydrochloride and 3-aminopyridine in DMF containing EtN(CHMe<sub>2</sub>)<sub>2</sub> and catalytic DMAP. The affinity of I for  $\alpha$ 7-nAChR was determined (no data).

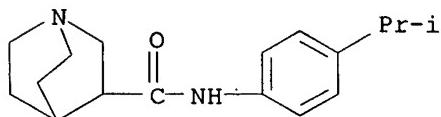
IT 552832-93-6P, N-(4-Isopropylphenyl)quinuclidine-3-carboxamide hydrochloride

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of monocyclic N-aryl amides for improvement of the perception and memory enhancement)

RN 552832-93-6 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-[4-(1-methylethyl)phenyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1991:199358 CAPLUS

DOCUMENT NUMBER: 114:199358

TITLE: EO-199, a specific antagonist of antiarrhythmic drugs: assessment by binding experiments and in vivo studies

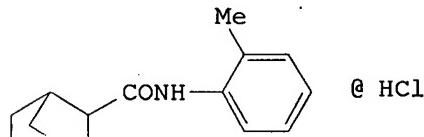
AUTHOR(S): Oppenheimer, Edna; Harel, Gideon; Lipinsky, Dafna; Sarne, Yosef

CORPORATE SOURCE: Sackler Fac. Med., Tel-Aviv Univ., Ramat-Aviv, 69978, Israel

SOURCE: Life Sciences (1991), 48(10), 977-85  
CODEN: LIFSAK; ISSN: 0024-3205

DOCUMENT TYPE: Journal  
LANGUAGE: English

GI



I

AB EO-199 (I), a demethylated analog of the novel class I antiarrhythmic drug EO-122, was found to antagonize the antiarrhythmic activity of EO-122 and that of procainamide (Class I). EO-199 did not block the activity of a class IB antiarrhythmic agent, lidocaine. EO-199 also displaced the specific binding of [<sup>3</sup>H]EO-122 to rat heart membranes similarly to procainamide, whereas lidocaine did not. The correlation between binding expts. and pharmacol: effects points to a possible subclassification of these drugs. The 2 chemical analogs EO-199 and EO-122, as well as procainamide (IA) but not lidocaine (IB), compete at the same site or the same state of the sodium channel. The availability of a specific antagonist might be useful for studying the mechanism of action of antiarrhythmic drugs as well as an antidote in cases of antiarrhythmics overdose intoxication.

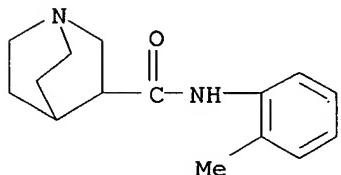
IT 133658-30-7, EO 199

RL: BIOL (Biological study)

(antiarrhythmic agents antagonism by, poisoning by antiarrhythmics in relation to)

RN 133658-30-7 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2-methylphenyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1990:69427 CAPLUS

DOCUMENT NUMBER: 112:69427

TITLE: Molecular modeling studies on class Ia and Ib antiarrhythmics. Model representations for differentiating binding sites

AUTHOR(S): Marrer, S.

CORPORATE SOURCE: Pharm. Inst., Freie Univ. Berlin, Berlin, Fed. Rep. Ger.

SOURCE: Pharmaceutica Acta Helveticae (1989), 64(12), 338-44

CODEN: PAHEAA; ISSN: 0031-6865

DOCUMENT TYPE: Journal

LANGUAGE: German

AB The mol. properties of quinidine, EO 122, and lidocaine were investigated using theor. mol. modeling. The binding patterns of the mols. were investigated by calculating interaction energies with a neg. charged fragment (receptor model). Based on these calcns. a model for the differentiation of class Ia and class Ib antiarrhythmic drugs could be deduced. The results fit the modulated receptor hypothesis. The mol. basis for the preferred affinity of quinidine to the open state of the sodium channel and the equal affinity of lidocaine to the open and inactivated state of the channel were defined.

IT 23581-62-6, EO-122

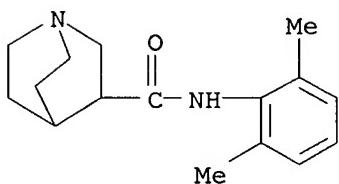
DL DTOT (Dose-Response)

(MOL. MODELING OF HEART SODIUM CHANNEL RECEPTOR INTERACTION WITH)

RN 23581-62-6 CAPLUS

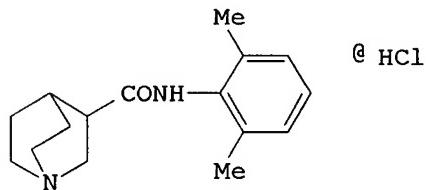
CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2,6-dimethylphenyl)-,

monohydrochloride (9CI) (CA INDEX NAME)



• HCl

L4 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 1989:400428 CAPLUS  
DOCUMENT NUMBER: 111:428  
TITLE: The specific binding of [<sup>3</sup>H]EO-122, a radiolabeled class I antiarrhythmic drug, to rat heart membranes  
AUTHOR(S): Oppenheimer, Edna; Meiri, Hamutal; Ori, Yaacov  
CORPORATE SOURCE: Sackler Fac. Med., Tel Aviv Univ., Ramat Aviv, 69978, Israel  
SOURCE: Journal of Molecular and Cellular Cardiology (1989), 21(2), 223-30  
CODEN: JMCDAY; ISSN: 0022-2828  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB [3H]EO-122 (I), a radiolabeled class I antiarrhythmic drug, was used to characterize a new specific binding system to rat heart membranes. The binding was saturable and competitive with unlabeled EO-122 and other antiarrhythmic drugs. In this system, [3H]EO-122 bound to 2 sites: site A with an apparent  $K_d$  of 33.5 nM,  $B_{max}$  of 1.05 pmol/mg protein and Hill coefficient  $nH = 4$  and site B with an apparent  $K_d$  of 233 nM,  $B_{max}$  of 5.7 pmol/mg protein and  $nH = 6$ . The binding to site B indicates that this site is pharmacol. relevant to known class IA antiarrhythmic drugs such as quinidine and procainamide. Lidocaine (class IB) did not interact with this site. Interpretation of the high Hill coefficient suggests that the binding of an antiarrhythmic drug to its pharmacol. relevant binding site exposes addnl. binding sites and/or modulates the affinity of adjacent binding sites.

IT 23581-62-6, EO 122

RL: PROC (Process)

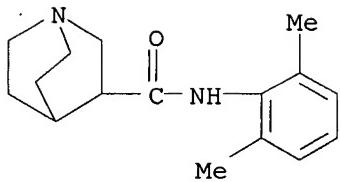
(binding of, by heart membrane)

RN 23581-62-6 CAPLUS

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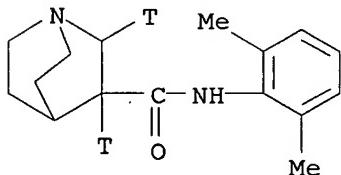
MONITORING OUTCOMES OF THE 1997 USA TRADE NAME

THE UNIVERSITY OF TORONTO LIBRARIES



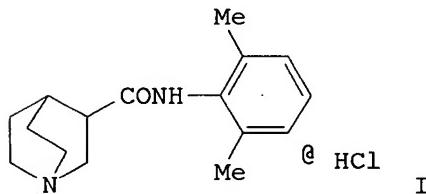
● HCl

IT 120949-68-0P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation and binding by heart membrane of)  
 RN 120949-68-0 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-2,3-dicarboxamide, N-(2,6-dimethylphenyl)-,  
 monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 1987:611641 CAPLUS  
 DOCUMENT NUMBER: 107:211641  
 TITLE: Electrophysiological effects of a novel antiarrhythmic drug, EO-122, on guinea pig ventricular muscle and isolated myocytes  
 AUTHOR(S): Binah, Ofer; Gilat, Eran; Rubinstein, Irit;  
 Oppenheimer, Edna  
 CORPORATE SOURCE: Rappaport Family Inst. Res. Med. Sci., Fac. Med.,  
 Haifa, 31096, Israel  
 SOURCE: Journal of Cardiovascular Pharmacology (1987), 10(3),  
 301-8  
 DOCUMENT TYPE: CODEN: JCPCDT; ISSN: 0160-2446  
 LANGUAGE: English  
 GI



AB The effects of EO-122 (I) on the electrophysiolog. properties of guinea pig papillary muscle and ventricular myocytes were investigated by means of

standard microelectrode and whole-cell recording techniques, resp. At the concentration range of 10-7-10-4 M (cycle length, 2000 ms), resting potential and

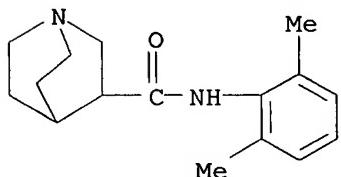
action potential duration (APD90) were not altered by the drug. Action potential amplitude and APD50 were reduced by 10-4 M, and Vmax was reduced by EO-122  $\geq$ 10-5 M. The effect of EO-122 on Vmax was use-dependent. At 10-6 and 10-5 M (cycle length, 2000 ms), the time constant for onset of block ( $\tau_{on}$ ) was 37.0 and 26.0 s, resp. The recovery kinetics from use-dependent block was not monoexponential, and the estimated "time constant" for recovery was 76.5 s. The effects of EO-122, 10-5 M on the membrane currents in ventricular myocytes were examined and it was found that the drug attenuated the slow inward current (Isi). The present study demonstrates that EO-122 blocks both the fast inward ( $\text{Na}^+$ ) and the slow inward ( $\text{Ca}^{2+}$ ) channels, and these effects are probably responsible for the antiarrhythmic effects of the drug.

IT 23581-62-6, EO-122

RL: BIOL (Biological study)  
(heart elec. activity response to, antiarrhythmic mechanism in relation to)

RN 23581-62-6 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2,6-dimethylphenyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1981:424851 CAPLUS

DOCUMENT NUMBER: 95:24851

TITLE: Process for the preparation of quinuclidine carboxylic acid derivatives

PATENT ASSIGNEE(S): Mundipharma A.-G., Switz.

SOURCE: Brit., 3 pp. Division of Brit. 1,578,421.

CODEN: BRXXAA

DOCUMENT TYPE: Patent

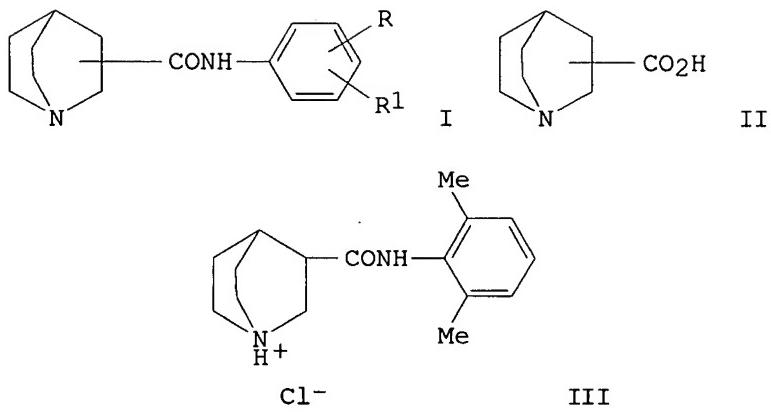
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 1578422	A	19801105	GB 1979-21014	19780119
IL 51296	A	19831031	IL 1977-51296	19770119
GB 1578421	A	19801105	GB 1978-2197	19780119
PRIORITY APPLN. INFO.:			IL 1977-51296	A 19770119
			GB 1978-2197	19780119

GI



AB The title compds. I (R, R1 = H, halo, C1-6 alkyl) were prepared by treating a quinuclidinecarboxylate II or its acid addition salts with H2NC6H3RR1 (R, R1 as before) in anhydrous alc.-free CHCl3 containing (COCl)2. E.g., 2.5 g of the HCl addition salt of II (CO2H group in 3-position) was refluxed 3 h in 150 mL anhydrous alc.-free CHCl3 containing 10 mL (COCl)2, then treated with 3

g

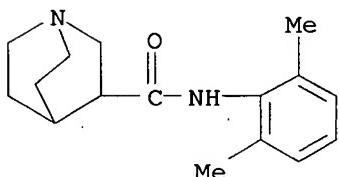
H2NC6H3Me2-2,6 in 100 mL CHCl3 (reflux, 6 h) to give, after work-up, 3 g (91%) III. III has useful antiarrhythmic properties (no data).

IT 23581-62-6P

RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation, of, as antiarrhythmic)

RN 23581-62-6 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2,6-dimethylphenyl)-,  
monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1980:561251 CAPLUS

DOCUMENT NUMBER: 93:161251

TITLE: A preclinical study of EO-122, a new lidocaine-like antiarrhythmic drug

AUTHOR(S): Oppenheimer, Edna; Kaplinsky, Eliezer; Kariv, Naam;  
Bruckstein, Rachel; Cohen, Sasson

CORPORATE SOURCE: Sackler Sch. Med., Tel-Aviv Univ., Kfar Saba, Israel

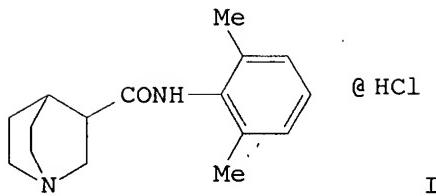
SOURCE: Angiology (1980), 31(6), 410-26

CODEN: ANGIAB; ISSN: 0003-3197

DOCUMENT TYPE: Journal

LANGUAGE: English

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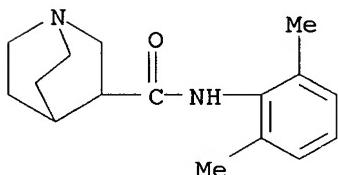
AB Restoration of normal sinus rhythm and suppression of ouabain-induced arrhythmia in cats and dogs, and of coronary occlusion-induced arrhythmia in dogs, followed a single i.v. injection of 1-3 mg EO 122 (I) [23581-62-6]/kg, with an onset of 2 min and a duration of 20-240 min. Occlusion-induced arrhythmia was also suppressed after an oral dose of 10-20 mg/kg, with an onset of 11-65 min and a duration of 25-120 min. Under similar conditions, lidocaine was either totally ineffective or of ultra-short duration. The bioavailability of EO-122 by the oral route exceeded 80% of the oral dose. Therapeutic blood concns. were in the range 0.5-7 µg/mL. At about 5 µg/mL, there was a slight depression of cardiac function in the anesthetized cat, but not in the conscious dog. In cats, complete A-V block occurred at concns. of 60-70 µg/mL. The i.v. LD<sub>50</sub> in mice was 22 mg/kg and in rabbits 8.5 mg/kg. No overt signs of neurotoxicity could be observed at any dose of EO-122. The pharmacokinetic profile of the drug fits a two-compartment open model, with t<sub>1/2</sub> ≈ 150 min.

IT 23581-62-6

RL: BIOL (Biological study)  
(heart arrhythmia response to)

RN 23581-62-6 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2,6-dimethylphenyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1979:92467 CAPLUS

DOCUMENT NUMBER: 90:92467

TITLE: Solvent-caused quaternization as a possible source of error in the mass spectral quantitation of tertiary amines. I. Methylene chloride quaternization  
Vincze, Adam; Gefen, Leon

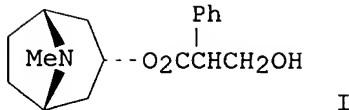
AUTHOR(S): Israel Inst. Biol. Res., Ness Ziona, Israel

CORPORATE SOURCE: Israel Journal of Chemistry (1978), 17(3), 236-8

SOURCE: CODEN: ISJCAT; ISSN: 0021-2148

DOCUMENT TYPE: Journal

G1



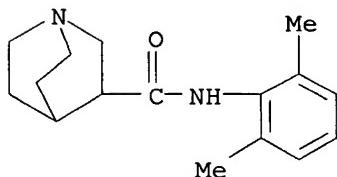
AB Basic tertiary amines such as atropine (I) [51-55-8] and derivs. of N-methylpiperidine and quinuclidine, tend to quaternize in CH<sub>2</sub>Cl<sub>2</sub> [75-09-2] at room temperature. The quaternary ammonium salts formed undergo various dequaternization reactions in the heated direct inlet probe of the mass spectrometer, giving rise to volatile tertiary amines that are different from the starting material and usually having higher mol. wts. Recorded spectra of such samples are a superposition of those of the various tertiary amines constituting the mixture. If just a few relevant and abundant ions in the mass spectrum of the original tertiary amine are monitored, as in quant. fragmentog. rather low results might be obtained. Moreover, the operator may be quite unaware of the fact that only part of the sample is being measured.

IT 69267-68-1

RL: RCT (Reactant); RACT (Reactant or reagent)  
(methylene chloride quaternization of, mass spectroscopic error in relation to)

RN 69267-68-1 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2,6-dimethylphenyl)- (9CI)  
(CA INDEX NAME)



L4 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1978:546786 CAPLUS

DOCUMENT NUMBER: 89:146786

TITLE: Antiarrhythmic quinuclidine carboxylic acid xylidide

INVENTOR(S): Oppenheimer, Edna; Kaplinsky, Eliezer; Cohen, Sasson

PATENT ASSIGNEE(S): Mundipharma A.-G., Switz.

SOURCE: Ger. Offen., 24 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

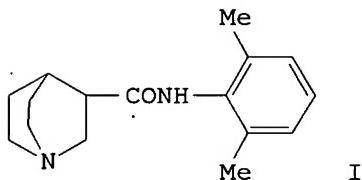
LANGUAGE: German

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2802208	A1	19780720	DE 1978-2802208	19780119
IL 51296	A	19831031	IL 1977-51296	19770119
ZA 7707476	A	19781025	ZA 1977-7476	19771215
FI 7703923	A	19780720	FI 1977-3923	19771223
ES 465827	A1	19790101	ES 1978-465827	19780107
SE 7800204	A	19780720	SE 1978-204	19780109
SE 443786	B	19860310		
DE 112786	A	19860310		
AU 1032409	A	19780120	AU 1978-32409	19780111
AU 519089	B2	19811105		
DK 7800264	A	19780720	DK 1978-264	19780118

DK 147180	B	19840507		
DK 147180	C	19841112		
NO 7800177	A	19780720	NO 1978-177	19780118
NO 148335	B	19830613		
NO 148335	C	19830921		
FR 2384499	A1	19781020	FR 1978-1354	19780118
FR 2384499	B1	19811030		
AT 7800353	A	19790815	AT 1978-353	19780118
AT 355586	B	19800310		
CA 1107734	A1	19810825	CA 1978-295163	19780118
JP 53109952	A	19780926	JP 1978-4764	19780119
JP 63008111	B	19880219		
PRIORITY APPLN. INFO.:			IL 1977-51296	A 19770119
OTHER SOURCE(S):	MARPAT	89:146786		
GI				

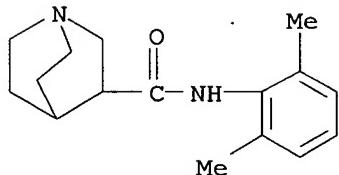


**AB** The title compound (**I**) was prepared in 91% yield by treating 3-quinuclidinecarboxylic acid-HCl with oxalyl chloride and 2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NH<sub>2</sub>. **I** has superior antiarrhythmic activity to lidocaine. The 2-quinuclidine analog of **I** is inactive and neurotoxic.

IT 23581-62-6P  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)  
(preparation and antiarrhythmic activity of)

RN 23581-62-6 CAPLUS

CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2,6-dimethylphenyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L4 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1970:78905 CAPLUS

DOCUMENT NUMBER: 72:78905

**TITLE:** 2 (and 3)-Quinuclidine carboxanilides

INVENTOR(S): **John C. Gammie**, **William L. Gammie**, **Robert W. Gammie**, **James E. Gammie**

卷二十一

PATENT ASSIGNEE(S): Aktiebolag Astra

PATENT ASSIGNEE(S): Aktieselskag  
SOURCE: Fr., 7 pp.

DOCUMENT TYPE: Patent  
 LANGUAGE: French  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

CODEN: FRXXAK

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1566045		19690502	FR	19680522
DE 1770414			DE	
FR 7713			FR	
GB 1176757			GB	
SE 331841			SE	
US 3579523		19710518	US	19680517
US 3726980		19730410	US	19701026
PRIORITY APPLN. INFO.:			SE	19670523

OTHER SOURCE(S): MARPAT 72:78905

GI For diagram(s), see printed CA Issue.

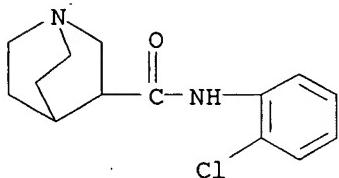
AB The title compds. (I) and (II), which have antiarrhythmic and local anesthetic effects, were prepared from derivs. of quinuclidine-2(or 3)-carboxylic acids (Renk, E.; et al., 1954). Thus, a mixture of 4.5 g Me quinuclidine-2-carboxylate, 2.9 g o-toluidine, and 0.1 g Na was kept 5 hr at 140° and worked up to give 2.1 g I (R1 = H, R2 = Me), m. 115.5-17° (aqueous EtOH). Similarly prepared were the following I (R1, R2, and m.p. HCl salt given): H, Cl, - [base m. 117-19.5° (aqueous EtOH)]; Me, Me, 223-5° (EtOH-isoPr2O); Me, Et, 209-11° (MeCOPr); Et, Et, 209.5-11.5° (MeCN). Also prepared were II (R = Cl), m. 166.5-8.5° (MeCOBu-iso), and II (R = H), m. 178-80° (MeCOBu-iso).

IT 26801-43-4P 26801-44-5P

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)

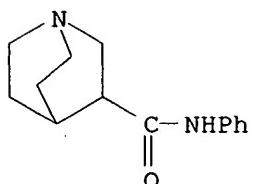
RN 26801-43-4 CAPLUS

CN 3-Quinuclidinecarboxanilide, 2'-chloro- (8CI) (CA INDEX NAME)



RN 26801-44-5 CAPLUS

CN 3-Quinuclidinecarboxanilide (8CI) (CA INDEX NAME)



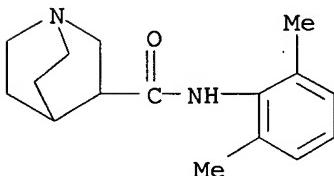
L4 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2007 ACS on STN  
 DOCUMENT NUMBER: 1000.161176 CAPLUS

DOCUMENT NUMBER:

11:011/0

TITLE: Some derivatives of quinuclidine-3-carboxylic acids  
 AUTHOR(S): Dahlbom, Richard; Dolby, Jorgen

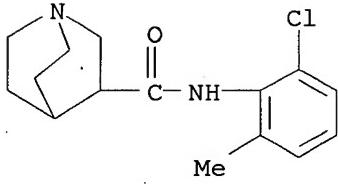
CORPORATE SOURCE: Farm. Fak. Stockholm, Stockholm, Swed.  
 SOURCE: Acta Pharmaceutica Suecica (1969), 6(2), 277-82  
 CODEN: APSXAS; ISSN: 0001-6675  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI For diagram(s), see printed CA Issue.  
 AB Me dehydroquinuclidine-3-carboxylate-HCl (Ia.HCl) (2.4 g.) in 20 ml. 33% aqueous MeNH<sub>2</sub> was kept 48 hrs. at room temperature, and worked up to give 54%  
 I (R = NHMe), m. 201-2°. Other amides similarly prepared were as follows [compound type, R (or R and R1), % yield, salt, and m.p. salt given]: II, NHMe, H, 47, HCl, 229-30°; III, NHEt, H, 40, HCl, 270-1°; I, NHEt, 63, oxalate, 169-72°; I, NHPr, 69, oxalate, 112-15°; and I, NHBu, 71, oxalate, 98-102°. Me quinuclidine-3-carboxylate-HCl (2.1 g.) in 20 ml. 20% HCl was refluxed 15 hrs., dried, 15 ml. SOCl<sub>2</sub> added, the mixture refluxed 3 hrs. and dried, 2.4 g. 2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NH<sub>2</sub> was added dropwise, 2.7 g. K<sub>2</sub>CO<sub>3</sub> and 20 ml. CHCl<sub>3</sub> were added, and the mixture refluxed 3 hrs. and worked up to give 60% II.HCl (R = 2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NH, R1 = H), m. 236-8°. The following compds. were similarly prepared [compound type, R (or R and R1), % yield, salt, and m.p. salt given]: II, pyrrolidine, H, 48,-(free base), 99-100°; I, NMe<sub>2</sub>, 54, HCl, 180-2°; I, NEt<sub>2</sub>, 32, HCl, 168-70°; I, pyrrolidino, 39,-(free base), 87-8.5°; I, piperidino, 36, HCl, 183-4°; II, 2-MeC<sub>6</sub>H<sub>4</sub>NH, H, 55,-(free base), 169-70°; II, 2,6-MeClC<sub>6</sub>H<sub>3</sub>NH, H, 52, HCl, 226-8°; I, 2-MeC<sub>6</sub>H<sub>4</sub>NH, 49, HCl, 208-9°; I, 2,6-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>NH, 45, HCl, 247-8°; and II, 2,6-MeClC<sub>6</sub>H<sub>3</sub>NH, 52, HCl, 236-7°. Ia was added to a solution of Na in the appropriate amino alc., and the mixture heated 6 hrs. at 70°/100 mm. to give the following II (R, R1, % yield, and m.p. given): O(CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>, OH, 73, 103-5°; O(CH<sub>2</sub>)<sub>2</sub>NEt<sub>2</sub>, OH, 73, 73-4.5°; pyrrolidinoethoxy, OH, 79, 90-1.5°; and piperidinoethoxy, OH, 82, 100-2°. III were prepared by treating the appropriate amino esters in Me<sub>2</sub>CO with MeI. The salt separated almost immediately and was collected and recrystd. from 90% EtOH. The following III were prepared (R, % yield, and m.p. given): NMe<sub>3</sub>, 95, 239-40°; NMeEt<sub>2</sub>, 92, 249-50°; N-methylpyrrolidino, 95, 247-8°; and N-methylpiperidino, 89, 248-9°. All the compds. were tested for pharmacol. and microbiol. activities, but showed no appreciable effects.  
 IT 23581-62-6P 23581-63-7P 23692-14-0P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation of)  
 RN 23581-62-6 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2,6-dimethylphenyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

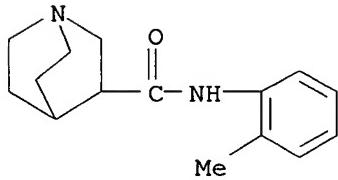
RN 23581-63-7 CAPLUS

(CA INDEX NAME)



● HCl

RN 23692-14-0 CAPLUS  
 CN 1-Azabicyclo[2.2.2]octane-3-carboxamide, N-(2-methylphenyl)- (9CI) (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 09:55:56 ON 14 MAY 2007)

FILE 'REGISTRY' ENTERED AT 09:56:11 ON 14 MAY 2007

L1 STRUCTURE uploaded  
 L2 3 S L1  
 L3 79 S L1 FULL

FILE 'CAPLUS' ENTERED AT 09:56:54 ON 14 MAY 2007

L4 13 S L3 FULL

=> FIL STNGUIDE

COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
69.45	241.76

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY	TOTAL SESSION
-10.14	-10.14

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LAST RELOADED: May 11, 2007 (20070511/UP).

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(FILE 'HOME' ENTERED AT 09:55:56 ON 14 MAY 2007)

FILE 'REGISTRY' ENTERED AT 09:56:11 ON 14 MAY 2007

L1 STRUCTURE uploaded  
 L2 3 S L1

L3 79 S L1 FULL

FILE 'CAPLUS' ENTERED AT 09:56:54 ON 14 MAY 2007  
L4 13 S L3 FULL

FILE 'STNGUIDE' ENTERED AT 09:58:02 ON 14 MAY 2007

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COST IN U.S. DOLLARS SINCE FILE TOTAL  
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FULL ESTIMATED COST 0.30 242.06  
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL  
ENTRY SESSION  
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NEWS 2 JAN 08        CHEMLIST enhanced with New Zealand Inventory of Chemicals  
NEWS 3 JAN 16        CA/CAplus Company Name Thesaurus enhanced and reloaded  
NEWS 4 JAN 16        IPC version 2007.01 thesaurus available on STN  
NEWS 5 JAN 16        WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data  
NEWS 6 JAN 22        CA/CAplus updated with revised CAS roles  
NEWS 7 JAN 22        CA/CAplus enhanced with patent applications from India  
NEWS 8 JAN 29        PHAR reloaded with new search and display fields  
NEWS 9 JAN 29        CAS Registry Number crossover limit increased to 300,000 in multiple databases  
NEWS 10 FEB 15       PATDPASPC enhanced with Drug Approval numbers  
NEWS 11 FEB 15       RUSSIAPAT enhanced with pre-1994 records  
NEWS 12 FEB 23       KOREAPAT enhanced with IPC 8 features and functionality  
NEWS 13 FEB 26       MEDLINE reloaded with enhancements  
NEWS 14 FEB 26       EMBASE enhanced with Clinical Trial Number field  
NEWS 15 FEB 26       TOXCENTER enhanced with reloaded MEDLINE  
NEWS 16 FEB 26       IFICDB/IFIPAT/IFIUDB reloaded with enhancements  
NEWS 17 FEB 26       CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases  
NEWS 18 MAR 15       WPIDS/WPIX enhanced with new FRAGHITSTR display format  
NEWS 19 MAR 16       CASREACT coverage extended  
NEWS 20 MAR 20       MARPAT now updated daily  
NEWS 21 MAR 22       LWPI reloaded  
NEWS 22 MAR 30       RDISCLOSURE reloaded with enhancements  
NEWS 23 APR 02       JICST-EPLUS removed from database clusters and STN  
NEWS 24 APR 30       GENBANK reloaded and enhanced with Genome Project ID field  
NEWS 25 APR 30       CHEMCATS enhanced with 1.2 million new records  
NEWS 26 APR 30       CA/CAplus enhanced with 1870-1889 U.S. patent records  
NEWS 27 APR 30       INPADOC replaced by INPADOCDB on STN  
NEWS 28 MAY 01       New CAS web site launched  
NEWS 29 MAY 08       CA/CAplus Indian patent publication number format defined  
NEWS 30 MAY 11       RDISCLOSURE on STN Easy enhanced with new search and display fields  
NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.  
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FILE 'HOME' ENTERED AT 10:22:15 ON 14 MAY 2007

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FILE LAST UPDATED: 13 May 2007 (20070513/ED)

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=> s nicotinic acetylcholine receptors  
37945 NICOTINIC  
1 NICOTINICS  
37946 NICOTINIC  
(NICOTINIC OR NICOTINICS)  
75959 ACETYLCHOLINE  
72 ACETYLCHOLINES  
75979 ACETYLCHOLINE  
(ACETYLCHOLINE OR ACETYLCHOLINES)  
641488 RECEPTORS  
L1 3210 NICOTINIC ACETYLCHOLINE RECEPTORS  
(NICOTINIC(W)ACETYLCHOLINE(W)RECEPTORS)

=> s l1 and memory?  
143306 MEMORY?  
L2 159 L1 AND MEMORY?

=> s l2 and py<2003  
22885320 PY<2003  
L3 60 L2 AND PY<2003

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L3 ANSWER 1 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2005:18847 CAPLUS  
DOCUMENT NUMBER: 142:233395  
TITLE: Multiple roles of cholinergic receptors in the  
olfactory bulb-toward a unifying hypothesis  
AUTHOR(S): Carleton, A.; Castillo, P. E.; Vincent, J.-D.; Lledo,  
P.-M.  
CORPORATE SOURCE: C.N.R.S., Institut de Neurobiologie Alfred Fessard,

SOURCE: Gif-sur-Yvette, 91198, Fr.  
Recent Research Developments in Neurochemistry (2002), 5, 159-168  
CODEN: RRDNFR

PUBLISHER: Research Signpost  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. The main olfactory bulb is the 1st site of olfactory information processing in the brain. It constitutes a critical relay between the olfactory epithelium and the olfactory cortex. A remarkable feature of this structure is its massive innervation by cholinergic inputs from the basal forebrain. In this review, we discuss the functional interaction between cholinergic inputs and the intrinsic bulbar circuitry. To determine the roles of acetylcholine in the olfactory bulb, we first characterized the effects of cholinergic agonists on both neural excitability and synaptic transmission. The diversity of targeted bulbar neurons by cholinergic inputs and their multiple effects will be briefly presented. In particular, we present evidence that nicotinic acetylcholine receptors excite both output neurons of the bulb, mitral cells, as well as interneurons located in the periglomerular regions. Interestingly, nicotine-induced responses in interneurons are short-lasting, whereas responses in mitral cells are long-lasting which suggests different consequences upon their resp. firing properties. As found for nicotine-induced responses, activation of muscarinic receptors triggers opposite effects for interneurons and mitral cells; it inhibits the firing rate of interneurons from a deeper layer, the granule cells, while at the same time it increases the degree of GABA release onto mitral cells. Thus, cholinergic signaling has multiple and opposing roles in the olfactory bulb neuronal network. Together, the direct excitation of relay bulbar neurons and inhibition of granule cells allow the ascending cholinergic system to exert a powerful facilitating influence over the transfer of olfactory information from the bulb to the cerebral cortex. In turn, by increasing GABA release onto mitral cells, the activation of muscarinic receptors allows the synchronization of a cluster of output neurons sharing the same cholinergic innervation. These findings on the cholinergic control of olfactory bulb output to central structures may guide future studies linking neuromodulators to cortical memory formation.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2003:494146 CAPLUS  
DOCUMENT NUMBER: 139:209108

TITLE: Effects of imidacloprid on the neural processes of memory in honey bees  
AUTHOR(S): Armengaud, C.; Lambin, M.; Gauthier, M.  
CORPORATE SOURCE: Laboratoire de Neurobiologie de l'Insecte, EA 3037, Universite Paul Sabatier Toulouse III, Toulouse, 31062, Fr.  
SOURCE: Honey Bees: Estimating the Environmental Impact of Chemicals (2002), 85-100. Editor(s): Devillers, James; Pham-Deleuge, Minh-Ha. Taylor & Francis Ltd.: London, UK.  
CODEN: 69EDMA; ISBN: 0-415-27518-0

DOCUMENT TYPE: Conference  
LANGUAGE: English

AB The cholinergic system in insects is the main target of insecticides. One class of mols., the neonicotinoids, induces direct activation of the neuronal nicotinic acetylcholine receptors (nAChRs). In the honey bee these receptors are mainly distributed in the olfactory pathways that link sensory neurons to antennal lobes and mushroom bodies. These structures seem to play an important rôle in olfactory conditioning. The authors have previously shown that cholinergic antagonists injected in different parts of the brain impaired

the formation and retrieval of olfactory memory. The authors then advanced the hypothesis that, through the activation of the nAChR, the neonicotinoid imidacloprid (IMI) would lead to facilitation of the memory trace. To test this hypothesis, IMI was applied topically upon the thorax and the effects were tested on the habituation of the proboscis extension reflex induced by repeated sugar stimulation of the antennae. Animals treated with IMI to a dose that did not affect sensory or motor functions needed fewer trials than nontreated animals to show a reflex inhibition. This effect can be interpreted as a learning facilitation. The authors developed a functional histochem. of cytochrome oxidase (CO) to reveal the brain targets of the drug in the honey bee brain. Following IMI injection, a CO staining increase, probably linked to an increase in metabolism, was observed in the antennal lobes. In integrative

structures, in particular the calyces of mushroom bodies, IMI exerted a facilitatory or inhibitory effect on neuronal metabolism depending on the dose. The brain targets of nicotinic ligands, including pesticides, can be compared by using this technique.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2003:121871 CAPLUS  
DOCUMENT NUMBER: 139:223424  
TITLE: Nicotinic cholinergic modulation: galantamine as a prototype  
AUTHOR(S): Woodruff-Pak, Diana S.; Lander, Cynthia; Geerts, Hugo  
CORPORATE SOURCE: Temple University and Albert Einstein Healthcare Network, Philadelphia, PA, USA  
SOURCE: CNS Drug Reviews (2002), 8(4), 405-426  
CODEN: CDREFB; ISSN: 1080-563X  
PUBLISHER: Neva Press  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Nicotinic acetylcholine receptor pharmacol. is becoming increasingly important in the clin. symptomatol. of neurodegenerative diseases in general and of cognitive and behavioral aspects in particular. In addition, the concept of allosteric modulation of nicotinic acetylcholine receptors has become a research focus for the development of therapeutic agents. In this review the scientific evidence for changes in nicotinic acetylcholine receptors in Alzheimer's disease is described. Within this context, the pharmacol. of galantamine, a recently approved drug for cognition enhancement in Alzheimer's disease, is reviewed along with preclin. studies of its efficacy on learning and memory. Galantamine modestly inhibits acetylcholinesterase and has an allosteric potentiating ligand effect at nicotinic receptors. The data collected in this review suggest that the unique combination of acetylcholinesterase inhibition and nicotinic acetylcholine receptor modulation offers potentially significant benefits over acetylcholinesterase inhibition alone in facilitating acetylcholine neurotransmission.

REFERENCE COUNT: 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:966636 CAPLUS  
DOCUMENT NUMBER: 138:219062  
TITLE: Nicotinic receptors in circuit excitability and epilepsy  
AUTHOR(S): Raggenbass, Mario; Bertrand, Daniel  
CORPORATE SOURCE: Department of Physiology, University Medical Center, Geneva, CH-1211, Switz.  
SOURCE: Journal of Neurobiology (2002), 53(4), 580-589  
CODEN: JNEUBZ; ISSN: 0022-3034

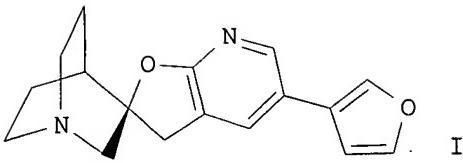
PUBLISHER: John Wiley & Sons, Inc.  
 DOCUMENT TYPE: Journal; General Review  
 LANGUAGE: English  
 AB A review. Neuronal nicotinic acetylcholine receptors belong to the family of excitatory ligand-gated channels and result from the assembly of five subunits. Functional heteromeric nicotinic receptors are present in the hippocampus and neocortex, thalamus, mesolimbic dopamine system and brainstem motor nuclei, where they may play a role, resp., in memory, sensory processing, addiction and motor control. Some forms of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) have been found to be associated with mutations in the genes coding for the  $\alpha$ 4 or  $\beta$ 2 subunits of the nicotinic receptor. Mutant receptors display an increased acetylcholine sensitivity with respect to normal receptors. Since the thalamus and the cortex are strongly innervated by cholinergic neurons projecting from the brainstem and basal forebrain, an imbalance between excitation and inhibition, brought about by the presence of mutant receptors, could generate seizures by facilitating and synchronizing spontaneous oscillations in thalamo-cortical circuits.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2002:927434 CAPLUS  
 DOCUMENT NUMBER: 138:14045  
 TITLE: Preparation of (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] as novel ligand for nicotinic acetylcholine receptors  
 INVENTOR(S): Phillips, Eifion  
 PATENT ASSIGNEE(S): AstraZeneca Ab, Swed.  
 SOURCE: PCT Int. Appl., 15 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002096912	A1	20021205	WO 2002-SE1031	20020529 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2455341	A1	20021205	CA 2002-2455341	20020529 <--
AU 2002303064	A1	20021209	AU 2002-303064	20020529 <--
EP 1397366	A1	20040317	EP 2002-731063	20020529
EP 1397366	B1	20070207		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CN 1512995	A	20040714	CN 2002-811049	20020529
BR 2002010075	A	20040817	BR 2002-10075	20020529
JP 2004532877	T	20041028	JP 2003-500091	20020529
NZ 529426	A	20050729	NZ 2002-529426	20020529
AT 353332	T	20070215	AT 2002-731063	20020529
ZA 2003008779	A	20050211	ZA 2003-8779	20031111
PRIORITY APPLN. INFO.:			US 2001-295206P	P 20010601
			WO 2002-SE1031	W 20020529

GI



AB The title compound I.2HCl, useful in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders (no biol. data given), was prepared by bromination of (R)-spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] followed by reacting the resulting 5'-bromo derivative with 3-furylboronic acid in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and Na<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O/EtOH/THF.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:927433 CAPLUS

DOCUMENT NUMBER: 138:14081

TITLE: Preparation of heteroaryl diazabicycloalkanes as central nervous system modulators

INVENTOR(S): Peters, Dan; Olsen, Gunnar M.; Nielsen, Elsebet Ostergaard; Ahring, Philip K.; Jorgensen, Tino Dyhring; Sloek, Frank Abildgaard

PATENT ASSIGNEE(S): Neurosearch A/S, Den.

SOURCE: PCT Int. Appl., 49 pp.

CODEN: PIXXD2

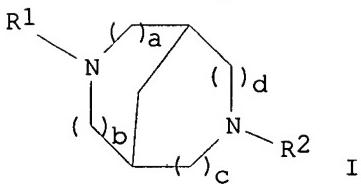
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002096911	A1	20021205	WO 2002-DK347	20020523 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
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AU 2002254880	A1	20021209	AU 2002-254880	20020523 <--
EP 1397365	A1	20040317	EP 2002-724151	20020523
EP 1397365	B1	20050216		
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JP 2004538268	T	20041224	JP 2003-500090	20020523
AT 289310	T	20050315	AT 2002-724151	20020523
US 2004147505	A1	20040729	US 2003-479348	20031201
PRIORITY APPLN. INFO.:			DK 2001-866	A 20010601
			WO 2002-DK347	W 20020523
OTHER SOURCE(S):	MARPAT	138:14081		
GI				



AB The present invention relates to novel diazabicycloalkanes (shown as I; a/b/c/d = 1,1,1,1, 1,1,1,2, 1,1,2,1, 0,2,0,2 and 0,0,2,2; see below for addnl. definitions of variables; e.g. 3-benzyl-7-(6-phenyl-3-pyridazinyl)-3,7-diazabicyclo[3.3.1]nonane), their labeled or unlabeled forms, any of their enantiomers, any mixture of enantiomers, or pharmaceutically acceptable salts thereof or a prodrug thereof, which are cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters. Due to their pharmacol. profile the compds. of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances. A diazabicycloalkane derivative = those represented by Formula I, by Formula II, by Formula III, by Formula IV, and by Formula V. For I: n = 1, 2 or 3; R1 = H, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkenylalkyl, alkynyl, alkynylalkyl, aryl, aralkyl or fluorescent group, which aryl groups may be substituted ≥1 times with substituents alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, methylenedioxy, hydroxy, alkoxy, alkoxyalkyl, alkoxyalkoxy, aryloxy, sulfhydryl, thioalkoxy, alkylcarbonyloxy, halogen, CF<sub>3</sub>, OCF<sub>3</sub>, CN, and nitro; and/or which aryl groups may be substituted with ≥1 fluorescent groups. R2 = a mono- or polycyclic aryl group, or a mono- or poly-heterocyclic group, which aryl and heterocyclic groups may be substituted ≥1 times with substituents alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, methylenedioxy, hydroxy, alkoxy, alkoxyalkyl, alkoxyalkoxy, aryloxy, sulfhydryl, thioalkoxy, alkylcarbonyloxy, halogen, CF<sub>3</sub>, OCF<sub>3</sub>, CN, and nitro; or which heterocyclic group may be substituted once with another mono- or poly-heterocyclic group, a mono- or polycyclic aryl group, or a mono- or polycyclic aralkyl group; and/or which heterocyclic group may be substituted with ≥1 fluorescent groups. Although the methods of preparation are not claimed, several example preps. of I and intermediates are included and about 20 I are listed in the claims. Results for tabulated for two I regarding in vitro inhibition of 3H-5-Hydroxytryptamine (3H-5-HT, serotonin) uptake in cortical synaptosomes (e.g. IC<sub>50</sub> = 0.022 μM for 3-benzyl-7-(2-quinolinyl)-3,7-diazabicyclo[3.3.1]nonane) and in vitro inhibition of 3H-cytisine binding (e.g. IC<sub>50</sub> = 0.0030 for 7-(6-chloro-3-pyridazinyl)-3,7-diazabicyclo[3.3.1]nonane).

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:913864 CAPLUS

DOCUMENT NUMBER: 138:164983

TITLE: Chronic fluoride toxicity decreases the number of nicotinic acetylcholine receptors in rat brain

AUTHOR(S): Long, Yi-Guo; Wang, Ya-Nan; Chen, Jia; Jiang, Su-Fen; Nordberg, Agneta; Guan, Zhi-Zhong

CORPORATE SOURCE: China, Department of Pathology, Guiyang Medical College, Guiyang, Guizhou, 550004, Peop. Rep. China

SOURCE: Neurotoxicology and Teratology (2002),  
24(6), 751-757  
CODEN: NETEEC; ISSN: 0892-0362

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In order to investigate the mol. mechanism(s) underlying brain dysfunction caused by chronic fluorosis, neuronal nicotinic acetylcholine receptors (nAChRs) in the brain of rats receiving either 30 or 100 ppm fluoride in their drinking water for 7 mo were analyzed in the present study employing ligand binding and Western blotting. There was a significant reduction in the number of [<sup>3</sup>H]epibatidine binding sites in the brain of rats exposed to 100 ppm fluoride, but no alteration after exposure to 30 ppm. On the other hand, the number of [<sup>125</sup>I] $\alpha$ -BTX binding sites was significantly decreased in the brains of rats exposed to both levels of fluoride. Western blotting revealed that the level of the nAChR  $\alpha$ 4 subunit protein in the brains of rats was significantly lowered by exposure to 100 ppm, but not 30 ppm fluoride; whereas the expression of the  $\alpha$ 7 subunit protein was significantly decreased by both levels of exposure. In contrast, there was no significant change in the level of the  $\beta$ 2 subunit protein in the brains of rats administered fluoride. Since nAChRs play major roles in cognitive processes such as learning and memory, the decrease in the number of nAChRs caused by fluoride toxicity may be an important factor in the mechanism of brain dysfunction in the disorder.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:839423 CAPLUS

DOCUMENT NUMBER: 139:94415

TITLE: The rationale behind cholinergic drug treatment for dementia related to cerebrovascular disease

AUTHOR(S): Grantham, C.; Geerts, H.

CORPORATE SOURCE: Janssen Research Foundation, Beerse, B-2340, Belg.

SOURCE: Journal of the Neurological Sciences (2002), 203-204, 131-136

CODEN: JNSCAG; ISSN: 0022-510X

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Common to all subtypes of dementia, including Alzheimer's disease (AD), and those associated cerebrovascular disease (CVD), Lewy body pathol. and Parkinson's disease, is degeneration of cholinergic neurotransmission. The cholinergic hypothesis of AD is based on evidence of reduced cholinergic markers and decreased nos. of cholinergic neurons and nicotinic acetylcholine receptors (nAChR) in the hippocampus and cortex of the brain-both areas associated with memory, learning and executive function impairments characteristic of cognitive decline in AD. There is growing evidence for the involvement of the cholinergic system in vascular dementia (VaD). Attention has, therefore, recently turned to the use of cholinergic treatments such as galantamine (Reminyl), which has demonstrated broad-spectrum and long-term efficacy in AD, for the treatment of patients with VaD or AD with CVD. Galantamine is both a moderate, reversible, competitive acetylcholinesterase inhibitor, and an allosteric modulator of nAChR. Recent evidence suggests that the unmatched efficacy of galantamine in cognitive as well as behavioral and functional symptoms in patients with AD, as well as those with VaD or AD with CVD, may at least partly result from its unique dual cholinergic mode of action. Here, the rationale for using galantamine to treat dementia related to CVD is discussed. In particular, some interesting findings are covered which indicate the potential of galantamine to modulate other neurotransmitter systems (e.g. serotonergic, dopaminergic), which may be of specific relevance in the behavioral symptoms of dementia related to CVD.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:795369 CAPLUS  
DOCUMENT NUMBER: 138:296914  
TITLE: Preclinical experiments on cognition enhancement in Alzheimer's disease: drugs affecting nicotinic acetylcholine receptors  
AUTHOR(S): Woodruff-Pak, Diana S.  
CORPORATE SOURCE: Department of Psychology, Temple University, Philadelphia, PA, USA  
SOURCE: Drug Development Research (2002), 56(3), 335-346  
CODEN: DDREDK; ISSN: 0272-4391  
PUBLISHER: Wiley-Liss, Inc.  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

AB A review. Nicotinic acetylcholine receptors (nAChRs) play a role in a variety of diseases of the central nervous system including Alzheimer's disease (AD). There is currently great interest in evaluating AD-related nAChR changes, and pharmacol. treatment of nAChR deficits is a promising therapy. In AD,  $\alpha$ 7 nAChRs remain relatively stable in contrast to  $\alpha$ 4 $\beta$ 2 nAChRs that are lost in substantial nos. However,  $\alpha$ 7 nAChRs may be functionally impaired in AD because  $\beta$ -amyloid, a major neuropathol. in AD, blocks  $\alpha$ 4 $\beta$ 2 and  $\alpha$ 7 nAChRs. Agonists selective to  $\alpha$ 7 or  $\alpha$ 4 $\beta$ 2 nAChRs are neuroprotective against  $\beta$ -amyloid. A preclin. test of cognition-enhancing drugs affecting nAChRs is eyeblink classical conditioning. This task is severely impaired in human probable AD patients and is impaired by antagonists to nAChRs. Three drugs with different mechanisms of action on nAChRs (partial  $\alpha$ 7 nAChR agonism [GTS-21], acetylcholinesterase inhibition and allosteric modulation [galantamine], nootropic activation [nefiracetam]) were tested in young and older rabbits using eyeblink classical conditioning. All three drugs ameliorated learning and memory impairments in older rabbits and reversed an antagonist to nAChRs in young rabbits. Galantamine, with its allosteric modulatory action, was the only drug that facilitated learning in young rabbits. On the basis of efficacy of these drugs that affect nAChRs in preclin. studies and in Phase I (GTS-21), Phase II (nefiracetam), or Phase III (galantamine) clin. trials, exploration of nAChRs as targets for therapeutic intervention via a number of different pathways seems warranted.

REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:739903 CAPLUS  
DOCUMENT NUMBER: 138:297468  
TITLE: Nonhalogenated anesthetic alkanes and perhalogenated nonimmobilizing alkanes inhibit  $\alpha$ 4 $\beta$ 2 neuronal nicotinic acetylcholine receptors  
AUTHOR(S): Raines, Douglas E.; Claycomb, Robert J.; Forman, Stuart A.  
CORPORATE SOURCE: Departments of Anesthesia, Harvard Medical School, Boston, MA, USA  
SOURCE: Anesthesia & Analgesia (Baltimore, MD, United States) (2002), 95(3), 573-577  
CODEN: AACRAT; ISSN: 0003-2999  
PUBLISHER: Lippincott Williams & Wilkins  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB The nonhalogenated anesthetic alkanes, cyclopropane and butane, do not enhance  $\gamma$ -aminobutyric acid-elicited GABAergic currents, suggesting

that these agents produce anesthesia via interactions with other mol. targets. Perhalogenated nonimmobilizing alkanes; such as 1,2-dichlorohexafluorocyclobutane and 2,3-dichlorooctafluorobutane, also fail to enhance GABAergic currents, but display specific behavioral effects that are distinct from those of structurally similar anesthetics. At concns. predicted to be anesthetic, 1,2-dichlorohexafluorocyclobutane and 2,3-dichlorooctafluorobutane produce amnesia but fail to produce immobility. Neuronal nicotinic acetylcholine (nACh) receptors are sensitive to many anesthetics and are thought to have an important role in learning and memory. The authors postulated that neuronal nACh receptors might mediate the common amnestic action of nonhalogenated and perhalogenated alkanes. To test the hypothesis that neuronal nACh receptors have a role in mediating the behavioral effects of general anesthetics and nonimmobilizers, the authors quantified the inhibitory potencies of nonhalogenated anesthetic alkanes and perhalogenated nonimmobilizing alkanes on currents mediated by  $\alpha 4\beta 2$  neuronal nACh receptors. The authors' studies reveal that anesthetics and nonimmobilizers significantly inhibit  $\alpha 4\beta 2$  neuronal nACh receptors at concns. that suppress learning and with potencies that correlate with their hydrophobicities. These results support the hypothesis that  $\alpha 4\beta 2$  neuronal nACh receptors mediate the amnestic actions of alkanes but not their immobilizing actions.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:266265 CAPLUS  
DOCUMENT NUMBER: 136:396280  
TITLE: Nicotine preconditioning antagonizes activity-dependent caspase proteolysis of a glutamate receptor  
AUTHOR(S): Meyer, Erin L.; Gahring, Lorise C.; Rogers, Scott W.  
CORPORATE SOURCE: Salt Lake City Veterans Affairs-Geriatrics Research, Education, and Clinical Center and the University of Utah School of Medicine, Salt Lake City, UT, 84132, USA  
SOURCE: Journal of Biological Chemistry (2002), 277(13), 10869-10875  
CODEN: JBCHA3; ISSN: 0021-9258  
PUBLISHER: American Society for Biochemistry and Molecular Biology  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Neuronal excitation is required for normal brain function including processes of learning and memory, yet if this process becomes dysregulated there is reduced neurotransmission and possibly death through excitotoxicity. Nicotine, through interaction with neuronal nicotinic acetylcholine receptors, possesses the ability to modulate neurotransmitter systems through numerous mechanisms that define this critical balance. We examined the modulatory role of nicotine in primary mixed cortical neuronal-glia cultures on activity-dependent caspase cleavage of a glutamate receptor, GluR1. We find that GluR1, but not GluR2 or GluR3, is a substrate for agonist ( $\alpha$ -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid)-initiated rapid proteolytic cleavage at aspartic acid 865 through the activation of caspase 8-like activity that is independent of membrane fusion and is not coincident with apoptosis. Dose-dependent nicotine preconditioning for 24 h antagonizes agonist-initiated caspase cleavage of GluR1 through a mechanism that is coincident with desensitization of both nAChR $\alpha 4\beta 2$  and nAChR $\alpha 7$  receptors and the delayed activation of a caspase 8-like activity. The modulation of GluR1 agonist-initiated caspase-mediated cleavage by nicotine preconditioning offers a novel insight into how this agent can impart its numerous effects on the nervous system.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:127283 CAPLUS  
DOCUMENT NUMBER: 136:395825

TITLE: Nicotine activates the extracellular signal-regulated kinase 1/2 via the  $\alpha 7$  nicotinic acetylcholine receptor and protein kinase A, in SH-SY5Y cells and hippocampal neurones

AUTHOR(S): Dajas-Bailador, F. A.; Soliakov, L.; Wonnacott, S.  
CORPORATE SOURCE: Department of Biology and Biochemistry, University of Bath, Bath, BA2 7AY, UK

SOURCE: Journal of Neurochemistry (2002), 80(3), 520-530

PUBLISHER: Blackwell Publishing Ltd.  
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Neuronal nicotinic acetylcholine receptors (nAChR) can modulate many cellular mechanisms, such as cell survival and memory processing, which are also influenced by the serine/threonine protein kinases ERK1/2. In SH-SY5Y cells and hippocampal neurons, nicotine (100  $\mu$ M) increased the activity of ERK1/2. This effect was Ca<sup>2+</sup> dependent, and prevented by the  $\alpha 7$  nAChR antagonist  $\alpha$ -bungarotoxin ( $\alpha$ -Bgt) and an inhibitor (PD98059) of the upstream kinase MEK. To determine the intervening steps linking Ca<sup>2+</sup> entry to MEK-ERK1/2 activation, inhibitors of Ca<sup>2+</sup>-dependent kinases were deployed. In SH-SY5Y cells, selective blockers for PKC (Ro 31-8220), CaM kinase II (KN-62) or PI3 kinase (LY 294002) failed to inhibit the nicotine-evoked increase in ERK1/2 activity. In contrast, two structurally different inhibitors of PKA (KT 5720 and H-89) completely prevented the nicotine-dependent increase in ERK1/2 activity. Inhibition of the nicotine-evoked increase in ERK1/2 activity by H-89 was also observed in hippocampal cultures. Down stream of PKA, the activity of B-Raf was significantly decreased by nicotine in SH-SY5Y cells, as determined by direct measurement of MEK1 phosphorylation or in vitro kinase assays, whereas the modulation of MEK1 phosphorylation by Raf-1 tended to increase. Thus, this study provides evidence for a novel signaling route coupling the stimulation of  $\alpha 7$  nAChR to the activation of ERK1/2, in a Ca<sup>2+</sup> and PKA dependent manner.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:106599 CAPLUS  
DOCUMENT NUMBER: 136:177889

TITLE: Absence of  $\alpha 7$ -containing neuronal nicotinic acetylcholine receptors does not prevent nicotine-induced seizures

AUTHOR(S): Franceschini, Davide; Paylor, Richard; Broide, Ron; Salas, Ramiro; Bassetto, Laura; Gotti, Cecilia; De Biasi, Mariella

CORPORATE SOURCE: Division of Neuroscience, Baylor College of Medicine, Houston, TX, 77030, USA

SOURCE: Molecular Brain Research (2002), 98(1,2), 29-40

PUBLISHER: Elsevier Science B.V.  
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Nicotine is the primary addictive component in tobacco, and at relatively low doses it affects cardiovascular responses, locomotor activity, thermoregulation, learning, memory, and attention. At higher doses nicotine produces seizures. The mechanisms underlying the

convulsive effects of nicotine are not known, but studies conducted on a number of inbred strains of mice have indicated a pos. correlation between the number of  $\alpha$ -bungarotoxin ( $\alpha$ -BTX) binding sites in the hippocampus and the sensitivity to nicotine-induced seizures. Because  $\alpha 7$ -containing neuronal nicotinic acetylcholine receptors (nAChRs) represent the major binding site for  $\alpha$ -BTX, mice lacking the  $\alpha 7$  nAChR subunit were predicted to be less sensitive to the convulsive effects of nicotine. To test this hypothesis, we injected nicotine i.p. in  $\alpha 7$  mutant mice and found that the dose-response curve for nicotine-induced seizures was similar in the  $\alpha 7$  +/+,  $\alpha 7$  +/- and  $\alpha 7$  -/- mice. The retained sensitivity to the convulsant effects of nicotine could not be explained by the presence of cholinergic compensatory mechanisms such as increases in mRNA levels for other nAChR subunits, or changes in binding levels or affinity for nicotinic ligands such as epibatidine and nicotine. These findings indicate that  $\alpha 7$  may not be necessary for the mechanisms underlying nicotine-induced seizures.

REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:38707 CAPLUS  
DOCUMENT NUMBER: 136:178264  
TITLE: Nicotinic acetylcholine receptor  $\alpha 7$  and  $\alpha 4\beta 2$  subtypes differentially control GABAergic input to CA1 neurons in rat hippocampus  
Alkondon, Manickavasagom; Albuquerque, Edson X.  
Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD, 21201, USA  
Journal of Neurophysiology (2001), 86(6), 3043-3055  
CODEN: JONEA4; ISSN: 0022-3077  
PUBLISHER: American Physiological Society  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB The hippocampus, a limbic brain region involved in the encoding and retrieval of memory, has a well-defined structural network assembled from excitatory principal neurons and inhibitory interneurons. Because the GABAergic interneurons form synapses onto both pyramidal neurons and interneurons, the activation of nicotinic acetylcholine receptors (nAChRs) present on certain interneurons could induce either inhibition or disinhibition in the hippocampal circuitry. To understand the role of nAChRs in controlling synaptic transmission in the hippocampus, the authors evaluated the magnitude of nAChR-modulated GABAergic postsynaptic currents (PSCs) in pyramidal neurons and various interneurons of the CA1 region. Using whole cell patch-clamp recording and post hoc identification of neuronal types in rat hippocampal slices, the authors show that brief (12-s) nAChR activation by ACh (1 mM) or choline (10 mM) enhances the frequency of GABAergic PSCs in both pyramidal neurons and CA1 interneurons. The magnitude of  $\alpha 7$  nAChR-mediated GABAergic inhibition, as assessed by the net charge of choline-induced PSCs, was highest in stratum lacunosum moleculare interneurons followed by pyramidal neurons and s. radiatum interneurons. In contrast, the magnitude of  $\alpha 4\beta 2$  nAChR-mediated GABAergic inhibition, as assessed by the difference between the net charge of PSCs induced by ACh and choline, was highest in pyramidal neurons followed by s. lacunosum moleculare and s. radiatum interneurons. The present results suggest that cholinergic cues transmitted via specific subtypes of nAChRs modify the synaptic function in the hippocampus by inducing a differential degree of GABAergic inhibition in the target neurons.  
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2002:38005 CAPLUS  
DOCUMENT NUMBER: 137:4375  
TITLE: Correlation of nicotinic receptor binding with clinical and neuropathological changes in Alzheimer's disease and dementia with Lewy bodies  
AUTHOR(S): Sabbagh, M. N.; Reid, R. T.; Hansen, L. A.; Alford, M.; Thal, L. J.  
CORPORATE SOURCE: Department of Neurosciences, UCSD, La Jolla, CA, USA  
SOURCE: Journal of Neural Transmission (2001), 108(10), 1149-1157  
CODEN: JNTRF3; ISSN: 1435-1463  
PUBLISHER: Springer-Verlag Wien  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB We investigated the relationship between the loss of nicotinic acetylcholine receptors (nAChR) and the cognitive decline or neuropathol. changes seen in Alzheimer's Disease (AD) and dementia with Lewy bodies (DLB). Midfrontal (MF) cortex of 31 AD, 24 DLB and 11 non-demented controls was examined Total plaque (TP), neuritic plaque (NP) and neurofibrillary tangle (NFT) counts were obtained. NAClR binding was assayed using  $^3$ H-epibatidine [ $^3$ H-EPI]. Last Blessed Information-Memory-Concentration scores (BIMC), Mini-Mental State Examination (MMSE), Mattis Dementia Rating Scale (DRS) scores were collected. There were no correlations between  $^3$ H-EPI binding and TP, NP, NFTs counts in either AD or DLB. Last BIMC, MMSE, DRS scores did not correlate with  $^3$ H-EPI binding in AD or DLB. Thus, decline in cognitive function does not correlate with loss of nAChR in DLB or AD at the end of life suggesting that later in these diseases, loss of nAChR binding is not a reliable marker of cognitive function in AD or DLB. Loss of nAChR activity does not appear to be related to plaques or NFTs in AD or DLB.  
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2001:711674 CAPLUS  
DOCUMENT NUMBER: 136:63964  
TITLE: SIB-1553A, ( $\pm$ )-4-{[2-(1-methyl-2-pyrrolidinyl)ethyl]thio}phenol hydrochloride, a subtype-selective ligand for nicotinic acetylcholine receptors with putative cognitive-enhancing properties: effects on working and reference memory performances in aged rodents and nonhuman primates  
AUTHOR(S): Bontempi, Bruno; Whelan, Kevin T.; Risbrough, Victoria B.; Rao, Tadimeti S.; Buccafusco, Jerry J.; Lloyd, G. Kenneth; Menzaghi, Frederique  
CORPORATE SOURCE: Merck Research Laboratories, La Jolla, CA, USA  
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 299(1), 297-306  
CODEN: JPETAB; ISSN: 0022-3565  
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Preclin. and clin. data have suggested the potential use of nicotinic acetylcholine receptor (nAChR) ligands for treating cognitive dysfunction associated with neurodegenerative diseases, such as Alzheimer's disease. SIB-1553A, ( $\pm$ )-4-{[2-(1-methyl-2-pyrrolidinyl)ethyl]thio}phenol hydrochloride, a novel nAChR ligand with predominant agonist subtype selectivity for  $\beta$ 4 subunit-containing human neuronal nAChRs, was tested in a variety of cognitive paradigms in aged rodents and nonhuman primates after acute and repeated administration. S.c. administration of SIB-1553A improved delayed nonmatching to place performance in aged mice. In aged

rhesus monkeys, i.m. and oral administration of SIB-1553A improved choice accuracy in a delayed matching to sample task. SIB-1553A improved performances in these spatial and nonspatial working memory tasks but was less effective at improving performances in spatial reference memory tasks (i.e., aged rodents exposed to a discrimination task in a T-maze or trained to locate a hidden platform in a water maze). These data suggest that SIB-1553A has a predominant effect on attention/working memory processes. SIB-1553A also induced the release of acetylcholine in the hippocampus of aged rats and was equally effective whether administered acutely or repeatedly (6 wk of daily s.c. administration). Thus, rats repeatedly treated with SIB-1553A exhibit neither tolerance nor sensitization to the effects of the compound. The SIB-1553A-induced cognitive improvement may be in part related to an increase in cholinergic function. The present study provides addnl. support for the use of subtype-selective nAChR ligands as a potential therapy for the symptomatic treatment of specific cognitive deficits (such as attention/working memory deficits) associated with aging and neurol. diseases.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:696995 CAPLUS

DOCUMENT NUMBER: 136:74

TITLE: Modulation of nicotinic receptor activity in the central nervous system: a novel approach to the treatment of Alzheimer disease

AUTHOR(S): Albuquerque, E. X.; Santos, M. D.; Alkondon, M.; Pereira, E. F. R.; Maelicke, A.

CORPORATE SOURCE: Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD, 21201, USA

SOURCE: Alzheimer Disease and Associated Disorders (2001), 15(Suppl. 1), S19-S25

CODEN: ADADE2; ISSN: 0893-0341

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Impaired cholinergic function in the central nervous system is an early feature of Alzheimer disease (AD). Currently, cholinergic deficit is usually corrected by increasing the amount of acetylcholine in the synapse by inhibiting acetylcholinesterase (AChE). One of the most consistent cholinergic deficits in AD is the reduced expression of nicotinic acetylcholine receptors (nAChR) in the brain. Since these receptors are essential for learning and memory, restoring nicotinic cholinergic function is a promising approach to treating AD. Allosteric modulation of nAChR is a novel approach, which circumvents development of tolerance through long-term use of conventional nicotinic agonists. Allosteric modulators interact with receptor-binding sites distinct from those capable of recognizing the natural agonist. Pos. allosteric modulation of nAChR activity has no effect on conductance of single channels; instead, by facilitating channel opening, it potentiates responses evoked by the interaction of the natural agonist with presynaptic and postsynaptic nAChR. Allosteric modulation of nAChR activity could therefore potentially produce a significant benefit in AD. One such allosteric modulator is galantamine. In addition to increasing nAChR activity, galantamine also inhibits AChE. This novel, dual mechanism of action distinguishes galantamine from many other AChE inhibitors. Galantamine has been shown to improve cognitive and daily function for at least 6 mo in placebo-controlled trials, and to maintain these functions at baseline levels for at least 12 mo in a 6-mo open-label extension study. Galantamine has pos. effects on nAChR expression, which are likely to contribute to its sustained efficacy in the treatment of AD patients.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2001:556715 CAPLUS  
DOCUMENT NUMBER: 135:236917  
TITLE: Timing and location of nicotinic activity enhances or depresses hippocampal synaptic plasticity  
AUTHOR(S): Ji, Daoyun; Lape, Remigijus; Dani, John A.  
CORPORATE SOURCE: Division of Neuroscience and Structural and Computational Biology and Molecular Biophysics Program, Baylor College of Medicine, Houston, TX, 77030, USA  
SOURCE: Neuron (2001), 31(1), 131-141  
CODEN: NERNET; ISSN: 0896-6273  
PUBLISHER: Cell Press  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB This study reveals mechanisms in the mouse hippocampus that may underlie nicotinic influences on attention, memory, and cognition. Induction of synaptic plasticity, arising via generally accepted mechanisms, is modulated by nicotinic acetylcholine receptors. Properly timed nicotinic activity at pyramidal neurons boosted the induction of long-term potentiation via presynaptic and postsynaptic pathways. On the other hand, nicotinic activity on interneurons inhibited nearby pyramidal neurons and thereby prevented or diminished the induction of synaptic potentiation. The synaptic modulation was dependent on the location and timing of the nicotinic activity. Loss of these synaptic mechanisms may contribute to the cognitive deficits experienced during Alzheimer's diseases, which is associated with a loss of cholinergic projections and with a decrease in the number of nicotinic receptors.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 19 OF 60 CAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 2001:549716 CAPLUS  
DOCUMENT NUMBER: 136:273036  
TITLE: Post-stroke dementia: Nootropic drug modulation of neuronal nicotinic acetylcholine receptors  
AUTHOR(S): Zhao, Xilong; Yeh, Jay Z.; Narahashi, Toshio  
CORPORATE SOURCE: Department of Molecular Pharmacology and Biological Chemistry, Northwestern University Medical School, Chicago, IL, 60611, USA  
SOURCE: Annals of the New York Academy of Sciences (2001), 939(Neuroprotective Agents), 179-186  
CODEN: ANYAA9; ISSN: 0077-8923  
PUBLISHER: New York Academy of Sciences  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Nefiracetam is a new pyrrolidone nootropic drug that is being developed for clin. use in the treatment of post-stroke vascular-type and Alzheimer's-type dementia. Among a few neuroreceptors that have been identified as potential targets of nootropics, neuronal nicotinic acetylcholine receptors (nnAChRs) are deemed the most important since they are related to learning, memory, and Alzheimer's disease dementia. We have recently found potent stimulating action of nefiracetam on nnAChRs. Rat cortical neurons in long-term primary culture expressed nnAChRs. Whole-cell patch clamp expts. revealed two types of currents induced by ACh,  $\alpha$ -bungarotoxin ( $\alpha$ -BuTX)-sensitive, rapidly desensitizing,  $\alpha 7$ -type currents and  $\alpha$ -BuTX-insensitive, slowly desensitizing,  $\alpha 4\beta 2$ -type currents. Although  $\alpha 7$ -type currents were only weakly inhibited by nefiracetam,  $\alpha 4\beta 2$ -type currents were potently and efficaciously potentiated by nefiracetam. Nefiracetam at 0.1 nM reversibly potentiated

ACh-induced currents to 200-300% of control. Very high concns. (about 10  $\mu$ M) also potentiated these currents, but to a lesser extent, indicative of the bell-shaped dose-response relation known to occur for nefiracetam, even in animal behavior expts. Three specific inhibitors of each of PKA and PKC did not prevent nefiracetam from potentiating ACh-induced currents, indicating that these protein kinases are not involved in nefiracetam action. Pretreatment with pertussis toxin did not alter nefiracetam potentiation, indicating Gi/Go proteins are not involved. Pretreatment with cholera toxin did abolish nefiracetam potentiation. Thus, nefiracetam potentiation is mediated via Gs proteins. In conclusion, nefiracetam stimulates  $\alpha 4\beta 2$ -type nAChRs via Gs proteins at nanomolar concns. The potentiation of  $\alpha 4\beta 2$ -type nAChRs is thought to be at least partially responsible for cognitive enhancing action.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2001:436604 CAPLUS

DOCUMENT NUMBER: 135:178986

TITLE:  $\beta$ -Amyloid activates the mitogen-activated protein kinase cascade via hippocampal  $\alpha 7$  nicotinic acetylcholine receptors: in vitro and in vivo mechanisms related to Alzheimer's disease

AUTHOR(S): Dineley, Kelly T.; Westerman, Marcus; Bui, Duy; Bell, Karen; Ashe, Karen Hsiao; Sweatt, J. David

CORPORATE SOURCE: Division of Neuroscience, Baylor College of Medicine, Houston, TX, 77030, USA

SOURCE: Journal of Neuroscience (2001), 21(12), 4125-4133

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LANGUAGE: English

AB Alzheimer's Disease (AD) is the most common of the senile dementias, the prevalence of which is increasing rapidly, with a projected 14 million affected worldwide by 2025. The signal transduction mechanisms that underlie the learning and memory derangements in AD are poorly understood.  $\beta$ -Amyloid ( $A\beta$ ) peptides are elevated in brain tissue of AD patients and are the principal component of amyloid plaques, a major criterion for postmortem diagnosis of the disease. Using acute and organotypic hippocampal slice preps., the authors demonstrate that  $A\beta$  peptide 1-42 ( $A\beta 42$ ) couples to the mitogen-activated protein kinase (MAPK) cascade via  $\alpha 7$  nicotinic acetylcholine receptors (nAChRs). In vivo elevation of  $A\beta$ , such as that exhibited in an animal model for AD, leads to the upregulation of  $\alpha 7$  nAChR protein.  $\alpha 7$  NACR upregulation occurs concomitantly with the downregulation of the 42 kDa isoform of extracellular signal-regulated kinase (ERK2) MAPK in hippocampi of aged animals. The phosphorylation state of a transcriptional mediator of long-term potentiation and a downstream target of the ERK MAPK cascade, the cAMP-regulatory element binding (CREB) protein, were affected also. These findings support the model that derangement of hippocampus signal transduction cascades in AD arises as a consequence of increased  $A\beta$  burden and chronic activation of the ERK MAPK cascade in an  $\alpha 7$  nAChR-dependent manner that eventually leads to the downregulation of ERK2 MAPK and decreased phosphorylation of CREB protein.

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